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(54) Title: USE OF COMPUTATIONALLY DERIVED PROTEIN STRUCTURES OF GENETIC POLYMORPHISMS IN PHARMACOGENOMICS AND CLINICAL APPLICATIONS

(57) Abstract: Provided herein are computer-based methods for generating and using three-dimensional (3-D) structural models of target molecules and databases containing the models. The targets can be protein structural variants derived from genes containing polymorphisms. The models are generated using molecular modeling techniques and are used in structure-based drug design studies for identifying drugs that bind to particular structural variants in structure-based drug design studies, for designing allele-specific drugs and population-specific drugs and for predicting clinical responses in patients. Computer-based methods for predicting drug resistance or sensitivity via computational phenotyping are also provided. Databases containing protein structural variant models are also provided.

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USE OF COMPUTATIONALLY DERIVED PROTEIN STRUCTURES OF GENETIC POLYMORPHISMS IN PHARMACOGENOMICS AND CLINICAL APPLICATIONS

RELATED APPLICATIONS

Benefit of priority to the following applications is claimed herein:
U.S. application Serial No. 09/438,566 to Kalyanaraman Ramnarayan,
Edward T. Maggio and P. Patrick Hess, filed November 10, 1999 entitled
"USE OF COMPUTATIONALLY DERIVED PROTEIN STRUCTURES OF
GENETIC POLYMORPHISMS IN PHARMACOGENOMICS FOR DRUG

10 DESIGN AND CLINICAL APPLICATIONS"; and U.S. application Serial No.
(Attorney Dkt. No. 24737-1906B) to Kalyanaraman Ramnarayan, Edward
T. Maggio and P. Patrick Hess, filed November 1, 2000, entitled "USE OF
COMPUTATIONALLY DERIVED PROTEIN STRUCTURES OF GENETIC
POLYMORPHISMS IN PHARMACOGENOMICS FOR DRUG DESIGN AND

15 CLINICAL APPLICATIONS."

Where permitted the above-noted applications are incorporated by reference in their entirety. Also incorporated by reference in its entiretly is U.S. application Serial No. (attorney docket no. 24737-1906C), filed November 10, 2000, to entitled "USE OF COMPUTATIONALLY DERIVED PROTEIN STRUCTURES OF GENETIC POLYMORPHISMS IN PHARMACOGENOMICS AND CLINICAL APPLICATIONS."

Incorporation by reference of Tables provided on Compact Disks

For US purposes and where permitted, an electronic version on compact disk (CD) ROM of Tables 4 and 5, which set forth coordinates for three-dimensional structures of proteins in the database described herein is filed herewith, and, where permitted and for US purposes, the contents thereof is incorporated by reference in its entirety. Table 4 is the HIV reverse transcriptase coordinates, and Table 5 is the HIV protease coordinates. The files that contain Table 4 are entitled 1906TAB.PC1 and 1906TAB.PC2, created on November 10, 2000, and are 59,538 kilobytes

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and 304 kilobytes, respectively, and the file that contains Table 5 is entitled 1906TAB.PC3, created on November 10, 2000, and contains 11,413 kilobytes.

FIELD OF THE INVENTION

The present invention is related to computer-based methods and relational databases that use three-dimensional (3-D) protein structural models derived from genetic polymorphisms in the areas of computer-assisted drug design and the prediction of clinical responses in patients.

BACKGROUND OF THE INVENTION

Recent advances in molecular biology, such as the discovery and identification of large numbers of genes and the sequences thereof encoded in the genomes of humans, other mammals and infectious disease agents, have contributed to the identification of a large number of proteins, biological receptors and other macromolecules and complexes that are promising therapeutic targets. Based on the information derived from the gene sequences, the three-dimensional (3-D) molecular structures of the corresponding target proteins or receptors can be determined.

Since 3-D protein structure is related to biological function,
structure-based drug design is an increasingly useful methodology that
has made a great impact in the design of biologically active lead
compounds. Drug designers can design and screen potential new drugs
via computational methods, such as docking or binding studies, before
actually beginning patient testing. These experiments can be performed
in silico at a tiny fraction of the clinical cost.

The resulting molecules, while serving as lead compounds, often have unpredictable effects when employed in clinical trials. In addition, it has been observed that existing drugs with known clinical efficacy far often fail to achieve beneficial results when given to particular patients, or

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particular subpopulations, such as ethnic groups, of patients. Genetic stratification of a population can be the difference between drug failure and drug approval. Hence there is a need to develop methods to improve the drug discovery process. Therefore, it is an object herein to provide, among a variety of benefits, methods and products that address and solve these problems. In particular, it is an object herein to provide computationally-based methods for drug design, clinical testing protocols, identification of new drug candidates and drug therapies; for predicting drug sensitivity and resistance and other methods.

10 SUMMARY OF THE INVENTION

Provided herein are computer-based methods for generating and using three-dimensional (3-D) structural models of target biomolecules, particularly polymorphic and allelic variants. Also provided herein are databases that contain the sequences of such variants and also the 3-D structure of the variants for use with the methods.

Genetic polymorphisms arise, for example, as a result of gene sequence differences or as a result of post-translational modifications, including glycosylation. Hence genetic polymorphisms are manifested as gene products and proteins having variant structures. The variant structures result in differences in biological responses among the originating organisms. These differences in response, include, but are not limited to, differences among patient responses to a particular drug, effective dosage differences, and side effects. With respect to infectious organisms, some polymorphisms may arise that convey resistance or susceptibility to particular drug therapies by the altering the drug target structure.

Structural changes that arise as a result of genetic polymorphisms are not of unlimited variety, since 3-D structure impacts upon function. A knowledge of the repertoire of the fine differences among generally similar

-4-

3-D structures of particular proteins will permit design of drugs that bind to the most polymorphisms, drugs that induce the fewest side-effects, and drugs that are more effective against infectious agents. Knowledge of these structures ultimately will permit patient-specific or subpopulation-specific, such as ethic, age, or gender groups, design or selection of drugs.

The methods that are provided are for determining and using 3dimensional (3-D) protein structures that are derived from genetic polymorphisms to understand differences in biological activity that result from the polymorphisms, and to use this understanding to aid in the identification of potential new drug candidates and drug therapies. Also provided are methods for analyzing 3-D structures of protein structural variant targets derived from genetic polymorphisms to identify common structural features among the variants; methods for identifying structural changes in target proteins that are associated with multiple mutations arising from genetic polymorphisms and correlating this information with. biological activity; methods for using clinical data in conjunction with structural variants derived from genetic polymorphisms to understand and predict the pharmacological effects and clinical outcomes for drugs or potential drugs. Also provided are methods for generating 3-D protein structures derived from a given genotype to analyze protein-drug binding in silico to predict drug sensitivity or resistance. Also provided are databases that are used in methods provided herein and methods for generating the databases.

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In particular, target biomolecules are protein structural variants encoded by genes containing genetic variations, or polymorphisms. 3-D models of the structures of proteins are determined. The models are generated using molecular modeling techniques, such as homology modeling. The resulting models are then used in the methods provided

-5-

herein, which include structure-based drug design studies to design and identify drugs that bind to particular structural variants; structure-based drug design studies and to predict clinical responses in patients; and to design drugs that bind to all or a substantial portion of allelic variants of a target, to thereby increase the population of patients for whom a particular drug will be effective and/or to decrease the undesirable side-effects in a larger population.

Hence, computer-based methods of drug design based on target protein structural models derived from genetic polymorphisms are provided. The methods involve obtaining one, preferably two or more amino acid sequences of a target protein that is the product of a gene exhibiting genetic polymorphisms, where sequences represent different genetic polymorphisms, and generating 3-D protein structural variant models from the sequences. Structure-based drug design techniques are used to design potential new drug candidates or to suggest modifications to existing drugs based on predicted intermolecular interactions of the drugs or drug candidates with the models. Alternatively, drug molecules can be computationally docked with 3-D protein structural variant models based upon the sequences and energetically refined before performing structure-based drug design studies.

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In preferred embodiments, binding interactions between a drug or potential new drug candidate molecules and the structural variants are calculated in order to optimize intermolecular interactions between drug or potential drug molecules and the structural variant models or to select drug therapies for patients by determining a drug or drugs that have favorable binding interactions with the structural variant models.

In other embodiments, the binding interactions are determined by calculating the free energy of binding between the protein structural variant model and a docked molecule; and decomposing the total free

-6-

energy of binding based on the interacting residues in the protein active site.

After the protein structural variant models are generated, selected model structures are analyzed to determine common structural features that are conserved throughout the selected models. The conserved structural features can serve as scaffolds or pharmacophore models into which potential drugs or modified drugs are docked. For example, the selected model structures may represent the structural variants resulting from the most commonly occurring genetic polymorphisms or from genetic polymorphisms found in a specific patient subpopulation, such as a particular age group, ethnic or racial group, sex, or other subpopulation. Alternatively, the models may be selected based on clinical information, for example, the structural variants may be derived based on patients receiving a specific treatment regimen or exhibiting a particular clinical response to a given drug or on the duration of a particular drug treatment.

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The methods provided herein can be used for predicting clinical responses in patients based on genetic polymorphisms. For example, a structural variant model derived from a subject, such as a human patient, exhibiting a particular genetic polymorphism is generated and screened against a number of reference protein structural variant models derived from genetic polymorphisms of the same gene in other such subjects. In certain embodiments, the reference structures are stored in a database, preferably with observed clinical data associated with the structures, or polymorphisms. The structural variant model from the subject is compared to a reference structures, for example, by database searching, in order to identify reference structural variants that are similar to the model structure derived from the subject. Based on the premise that structurally similar targets will have similar clinical responses, a clinical outcome can be predicted for the patient based on the structures

-7-

identified through structural comparison or database searching. This information can also be used in the design and analysis of clinical trials; it can also be used for selecting appropriate therapies for a subject in instances in which the subject is a patient and the protein is a drug target.

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The methods are also used to design therapeutic agents that are active against biological targets that have become drug resistant, particularly due to genetic mutations. In certain embodiments, 3-D protein structural variant models are generated for a target protein in which genetic mutations have occurred and against which a given drug is no longer biologically active. The models are compared to 3-D protein structural variant models of the target protein against which the drug has biological activity in order to identify structural differences between the susceptible and resistant targets. The differences can be used to understand the structural contributions to drug resistance, and this information can be utilized in structure-based drug design calculations to identify new drugs or modifications to the existing drug that circumvent the resistance problem.

A computer-based method for identifying compensatory mutations in a target protein is also provided. The method involves obtaining the amino acid sequence of a target protein containing multiple amino acid mutations that is expressed in a patient, where the structure of a form of the target protein that responds to a particular drug, including the active site, has been structurally characterized; generating a 3-D structural model of the mutated protein; comparing the structure of the mutated protein with the form of the protein that responds to the drug to identify structural differences and/or similarities arising from the mutations; comparing the biological activities of the drug against the mutated protein and the form of the protein that responds to the drug to determine the

-8-

effects of the mutations on drug response; and identifying the mutations in the protein that affect biological activity based on the comparisons. The target biolmolecules can also be used in a method referred to herein as computational phenotyping to predict drug sensitivity or resistance for a given genotype. These computer-based method for identifying phenotypes in silico are provided. The methods involve obtaining from a patient/specimen, such as a body fluid or tissue sample, including blood, cerebral spinal fluid, urine, saliva, sweat and tissue samples, the amino acid sequence of a target protein; generating a 3-D structural model of the target protein; performing protein-drug binding analyses; and predicting drug sensitivity or resistance based on the protein-drug binding analyses.

Molecular structure databases containing protein structural variant models produced by the methods are also provided. The databases may also contain biological or clinical data associated with the structural variants. The databases can be interfaced to a molecular graphics package for visualization and analysis of the 3-D molecular structural models. In particular, databases containing the 3-D structures of polymorphic variants of selected target genes, particularly pharmaceutically significant genes with pharmaceutically significant gene products, such as proteases and polymerases, including reverse transcriptases, and receptors, such as cell surface receptors, are provided. The databases may be stored an provided on any suitable medium, including, but are not limited to, floppy disks, hard drives, CD-ROMS and DVDs.

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Also provided are relational databases for managing and using information relating to genetic polymorphisms. The databases contain 3-D molecular coordinates for structural variants derived from genetic polymorphism, a molecular graphics interface for 3-D molecular structure

visualization, computer functionality for protein sequence and structural analyses and database searching tools. The databases may further include observed clinical data associated with the genetic polymorphism. The databases provide a means to design the allele-specific drugs and also to identify among alleles common or conserved structural features that can serve as the target for drug design.

The databases can also be used for identification of invariant residues and regions of a target biomoleucle, such as an HIV protease or reverse transcriptase. The identified invariant regions are then used to computationally screen compounds, preferably small molecules by assessing binding interactions. The compounds so-identified serve as candidates for drugs that will be effective for a larger proporation of a population or against a broader range of variants of a pathogen, where the target protein is from a pathogens.

Systems, including computers, containing the databases also are provided herein. Any computer known to those of skill in the art for maintaining such databases is contemplated. User interfaces for accessing and manipulating the databases and content thereof are also provided.

20 BRIEF DESCRIPTION OF THE DRAWINGS

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- FIG. 1 illustrates a method for creating a protein structural variant relational database.
- FIG. 2 is a flow chart that describes one method used to generate structural variant models derived from genetic polymorphisms and to use the models in structure-based drug design studies.
- FIG. 3 is a flow chart that describes an alternative method used to generate structural variant models derived from genetic polymorphisms and to use the models in structure-based drug design studies.

WO 01/35316

PCT/US00/30863

- FIG. 4 shows the correlation between experimental and calculated changes of binding energy upon ligand modifications in the binding site of NS3.
- FIG. 5 shows a comparison of calculated *versus* experimental binding free energy changes for complexes of the tumor necrosis factor (TNF) receptor with different inhibitors.
 - FIG. 6 shows the HIV PR inhibitors approved by the FDA.
- FIG. 7 shows the frequency versus amino acid residue plot of HIV PR.
- FIG. 8 shows frequency analysis of 10591 HIV PR Sequences, where ResNum is the residue number; TotOcc is the total occurrence of the mutation; Dist is the distance of the mutating residue from approximate center of active site (Asp28); WtAA is the amino acid in the wild type protein; NumMut is the number of mutations; and MutList is a list of amino acid mutations.
 - FIG. 9 is a block diagram of an exemplary computer.
 - FIG. 10 is a graphical representation of a relational database.
 - FIG. 11 is a tabulation of the 3-D coordinates of a representative entry in a database that includes 3-D structures.

20 DETAILED DESCRIPTION OF THE INVENTION

A. Definitions

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- B. Computer-based methods of drug design based on genetic polymorphisms
- 25 1. Methods for obtaining amino acid sequences of a target protein
 - 2. Generation of 3-D protein structural variant models
 - a. Homology Modeling
 - b. Ab initio generation of 3-D structures
 - c. Crystal structures
 - 3. Use of 3-D structural variant models in drug design
 - a. Selection of relevant structural variants
 - b. Drug design
 - c. Computational docking

-11-

d. Free energy of binding studies

C. Applications of computer-based methods

5 1. Genetic polymorphisms and structure-based drug design

2. Drug resistance

3. Identification of conserved structural features or pharmacophores

4. Identification of compensatory structural changes

5. Clinical Applications

D. Creation of 3-D Structural Polymorphism Databases

1. Exemplary Databases and generation thereof

2. Computer systems and Database

E. Computational phenotyping

A. Definitions

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Unless defined otherwise, all technical and scientific terms used
herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents, patent applications, published patent applications and publications referred to herein are, unless noted otherwise, incorporated by reference in their entirety. In the event a definition in this section is not consistent with definitions elsewhere, the definition set forth in this section will control.

As used herein, polymorphism refers to a variation in the sequence of a gene in the genome amongst a population, such as allelic variations and other variations that arise or are observed. Genetic polymorphisms refers to the variant forms of gene sequences that can arise as a result of nucleotide base pair differences, alternative mRNA splicing or post-translational modifications, including, for example, glycosylation. Thus, a polymorphism refers to the occurrence of two or more genetically determined alternative sequences or alleles in a population. These differences can occur in coding and non-coding portions of the genome, and can be manifested or detected as differences in nucleic acid

-12-

sequences, gene expression, including, for example transcription, processing, translation, transport, protein processing, trafficking, DNA synthesis, expressed proteins, other gene products or products of biochemical pathways or in post-translational modifications and any other differences manifested among members of a population. A single nucleotide polymorphism (SNP) refers to a polymorphism that arises as the result of a single base change, such as an insertion, deletion or change in a base.

A polymorphic marker or site is the locus at which divergence occurs. Such site may be as small as one base pair (an SNP).

Polymorphic markers include, but are not limited to, restriction fragment length polymorphisms, variable number of tandem repeats (VNTR's), hypervariable regions, minisatellites, dinucleotide repeats, trinucleotide repeats, tetranucleotide repeats and other repeating patterns, simple sequence repeats and insertional elements, such as Alu. Polymorphic forms also are manifested as different mendelian alleles for a gene.

Polymorphisms may be observed by differences in proteins, protein modifications, RNA expression modification, DNA and RNA methylation, regulatory factors that alter gene expression and DNA replication, and any other manifestation of alterations in genomic nucleic acid or organelle nucleic acids.

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As used herein, structural variants proteins refer the variety of 3-D molecular structures or models thereof that result from the polymorphisms. These variants typically arise from transcription and translation of genes containing genetic polymorphisms, but also include diffentially glyocsylated or otherwise post-translationally modified variants that potentially exhibit differential interactions with drugs and drug candidates.

-13-

As used herein, binding interactions refer to atomic or physical interactions between molecules including, but not limited to binding free energy, hydrophobic interactions, electrostatic interactions, steric interactions and other interactions that are commonly considered by those of skill in the art to determine the affinity of one molecule to bind to another. Favorable binding interactions refer to binding interactions that promote physical or chemical associations between molecules.

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As used herein, a target protein is defined as a protein that is a receptor with which drugs or other ligands, such as small molecule or peptide agonists or antagonists or other proteins or biomacromolecules, such as DNA or RNA, interact to bring about a biological response.

As used herein, structure-based drug design refers to computer-based methods in which 3-D coordinates for molecular structures are used to identify potential drugs that can interact with a biological receptor. Examples of such methods include, but are not limited to, searching of small molecule libraries or databases, conformational searching of a ligand within an active site of identify biologically active conformations or computational docking methods.

As used herein, pharmacogenomics refers to study of the variablity of patient responses to drugs due to inherent genetic differences.

As used herein, computational docking refers to techniques wherein molecules, for example, a ligand and receptor or active site, are fitted together based on complementary interactions, for example, steric, hydrophobic or electrostatic interactions.

As used herein, energetic refinement refers to the use of molecular mechanics simulation techniques, such as energy minimization or molecular dynamics, or other techniques, such as quantum-based approaches, to "adjust" the coordinates of a molecular structural model to bring it into a stable, low energy, conformation. In molecular mechanics

-14-

simulations, the potential energy of a molecular system is represented as a function of its atomic coordinates along with a set of atomic parameters, called a forcefield. Energy minimization refers to a method wherein the coordinates of a molecular conformation are adjusted according to a target function to result in a lower energy conformation. Molecular dynamics refers to methods for simulating molecular motion by inputting kinetic energy into the molecular system corresponding to a specified temperature, and integrating the classical equations of motion for the molecular system. During a molecular dynamics simulation, a system undergoes conformational changes so that different parts of its accessible phase space are explored.

As used herein, clinical data refers to information obtained from patients pertaining to pharmacological responses of the patient to a given drug, including, but not limited to efficacy data, side effects, resistance or susceptibility to drug therapy, pharmacokinetics or clinical trial results.

As used herein, patient histories, include medical histories and other any information, such as parental medical histories, dates and places of birth of the patient and parents, number of siblings, number of children and other such data.

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As used herein, compensatory mutations are mutations that act in concert with active site mutations by compensating for functional deficits caused by changes or mutations that affect binding in the active site.

As used herein, a relational database is a collection of data items organized as a set of formally-described tables from which data can be accessed or reassembled in many different ways without having to reorganize the database tables. Such databases are readily available commercially, for example, from Oracle, IBM, Microsoft, Sybase, Computer Associates, SAP, or multiple other vendors.

-15-

As used herein, a phenotype refers to a set of parameters that includes any distinguishable trait of an organism. A phenotype can be physical traits and can be, in instances in which the subject is an animal, a mental trait, such as emotional traits. Some phenotypes can be determined by observation elicited by questionnaires or by referring to prior medical and other records. For purposes herein, a phenotype is a parameter around which the database can be sorted.

As used herein, genotype refers to a specific gene or totality of genetic information in a specific cell or organism.

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As used herein, haplotype refers refers to two or more polymorphism located on a single DNA strand. Hence, haplotyping refers to identification of two or more polymorphisms on a single DNA strand. Haplotypes can be indicative of a phenotype.

As used herein, a parameter is any input data that will serve as a basis for sorting the database. These parameters will include phenotypic traits, medical histories, family histories and any other such information elicited from a subject or observed about the subject. A parameter may describe the subject, some historical or current environmental or social influence experienced by the subject, or a condition or environmental influence on someone related to the subject. Paramaters include, but are not limited to, any of those described herein, and known to those of skill in the art.

As used herein, computational phenotyping, refers to computer-based processes that assess the phenotype resulting from a particular genotype. The phenotype describes observables, such as, but are not limited to, the structure of the encoded protein, its functional morphological and structural attributes. In particular, as contemplated herein, the phenotype that is assessed is the interaction of a protein with a particular compounds, particularly a drug. As exemplified herein, the

method provides a means to select an effective drug for a particular subjects, particularly mammals, or class thereof.

As used herein, a database refers to a collection of data; in this case data relating to polymorphic variants. Hence a database contains the nucleic acid sequences encoding the variants, or a portion of the variant, such as a portion contianing the active site or targetted site. Additionally, the database may contain other information related to each entry, including but are not limited to, the corresponding 3-D structure of the encoded protein (or a portion thereof) and information regaring the source of each sequence. Some of the entries in a database may be identical, and for purposes herein, a database contains at least 2 different entries, typically far more than 2 entries. The number of entries depends upon the protein of interest and variety and number of polymorphisms that exist. Generally a database will have at least 10 different entries, typically more than 100, more than 500, more than 1000, more than 2000, 3000, 4000, 5000, 8000, 10,000, 50,000, 100,000 and greater. Databases herein containing 20,000 entries and more have been generated and are exemplified herein.

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As used herein, a relational database stores information in a form representative of matrices, such as two-dimensional tables, including rows and columns of data, or higher dimensional matrices. For example, in one embodiment, the relational database has separate tables each with a parameter. The tables are linked with a record number, which also acts as an index. The database can be searched or sorted by using data in the tables and is stored in any suitable storage medium, such as floppy disk, CD rom disk, hard drive or other suitable medium.

As used herein, a profile refers to information relating to, but not limited to and not necessarily including all of, age, sex, ethnicity, disease

-17-

history, family history, phenotypic characteristics, such as height and weight and other relevant parameters.

As used herein, a biopolymer includes, but is not limited to, nucleic acid, proteins, polysaccharides, lipids and other macromolecules. Nucleic acids include DNA, RNA, and fragments thereof. Nucleic acids may be derived from genomic DNA, RNA, mitochondrial nucleic acid, chloroplast nucleic acid and other organelles with separate genetic material.

As used herein, a DNA or nucleic acid homolog refers to a nucleic acid that includes a preselected conserved nucleotide sequence. By the term "substantially homologous" is meant having at least 80%, preferably at least 90%, most preferably at least 95% homology therewith or a less percentage of homology or identity and conserved biological activity or function.

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As used herein, a receptor refers to a molecule that has an affinity for a given ligand. Receptors may be naturally-occurring or synthetic molecules. Receptors may also be referred to in the art as anti-ligands. As used herein, the terms, receptor and anti-ligand are interchangeable. Receptors can be used in their unaltered state or as aggregates with other species. Receptors may be attached, covalently or noncovalently, or in physical contact with, to a binding member, either directly or indirectly via a specific binding substance or linker. Examples of receptors, include, but are not limited to: antibodies, cell membrane receptors surface receptors and internalizing receptors, monoclonal antibodies and antisera reactive with specific antigenic determinants (such as on viruses, cells, or other materials), drugs, polynucleotides, nucleic acids, peptides, cofactors, lectins, sugars, polysaccharides, cells, cellular membranes, and organelles.

Examples of receptors and applications using such receptors, include but are not restricted to:

a) enzymes: specific transport proteins or enzymes essential to survival of microorganisms, which could serve as targets for antibiotic (ligand) selection;

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- b) antibodies: identification of a ligand-binding site on the antibody molecule that combines with the epitope of an antigen of interest may be investigated; determination of a sequence that mimics an antigenic epitope may lead to the development of vaccines of which the immunogen is based on one or more of such sequences or lead to the development of related diagnostic agents or compounds useful in therapeutic treatments such as for auto-immune diseases;
- c) nucleic acids: identification of ligand, such as protein or RNA, binding sites;
- d) catalytic polypeptides: polymers, preferably polypeptides, that are capable of promoting a chemical reaction involving the conversion of one or more reactants to one or more products; such polypeptides generally include a binding site specific for at least one reactant or reaction intermediate and an active functionality proximate to the binding site, in which the functionality is capable of chemically modifying the bound reactant (see, e.g., U.S. Patent No. 5,215,899);
- e) hormone receptors: determination of the ligands that bind with high affinity to a receptor is useful in the development of hormone replacement therapies; for example, identification of ligands that bind to such receptors may lead to the development of drugs to control blood pressure; and
- f) opiate receptors: determination of ligands that bind to the opiate receptors in the brain is useful in the development of less-addictive replacements for morphine and related drugs.

As used herein, prion refers to an infectious pathogen that causes central nervous system spongiform encephalopathies in humans and animals. No nucleic acid component is necessary for the infectivity of prion protein (see, e.g., U.S. Patent No. 5,808,969).

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As used herein, a ligand is a molecule that is specifically recognized by a particular receptor. Examples of ligands, include, but are not limited to, agonists and antagonists for cell membrane receptors, toxins and venoms, viral epitopes, hormones (e.g., steroids), hormone receptors, opiates, peptides, enzymes, enzyme substrates, cofactors, drugs, lectins, sugars, oligonucleotides, nucleic acids, oligosaccharides, proteins, and monoclonal antibodies.

As used herein, complementary refers to the topological compatibility or matching together of interacting surfaces of a ligand molecule and its receptor. Thus, the receptor and its ligand can be described as complementary, and furthermore, the contact surface characteristics are complementary to each other.

As used herein, a ligand-receptor pair or complex formed when two macromolecules have combined through molecular recognition to form a complex.

The terms "homology" and "identity" are often used interchangeably. In this regard, percent homology or identity may be determined, for example, by comparing sequence information using a GAP computer program. The GAP program utilizes the alignment method of Needleman and Wunsch (*J. Mol. Biol.* 48:443 (1970), as revised by Smith and Waterman (*Adv. Appl. Math.* 2:482 (1981). Briefly, the GAP program defines similarity as the number of aligned symbols (i.e., nucleotides or amino acids) which are similar, divided by the total number of symbols in the shorter of the two sequences. The preferred default parameters for the GAP program may include: (1) a unary comparison matrix (containing

-20-

a value of 1 for identities and 0 for non-identities) and the weighted comparison matrix of Gribskov and Burgess, *Nucl. Acids Res.* 14:6745 (1986), as described by Schwartz and Dayhoff, eds., *ATLAS OF PROTEIN SEQUENCE AND STRUCTURE*, National Biomedical Research Foundation, pp. 353-358 (1979); (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

Whether any two nucleic acid molecules have nucleotide sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% "identical" can be determined using known computer algorithms such as the "FAST A" program, using for example, the default parameters as in Pearson and Lipman, *Proc. Natl. Acad. Sci. USA 85*:2444 (1988). Alternatively the BLAST function of the National Center for Biotechnology Information database may be used to determine identity

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In general, sequences are aligned so that the highest order match is obtained. "Identity" per se has an art-recognized meaning and can be calculated using published techniques. (See, e.g.: Computational Molecular Biology, Lesk, A.M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D.W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part I, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991). While there exist a number of methods to measure identity between two polynucleotide or polypeptide sequences, the term "identity" is well known to skilled artisans (Carillo, H. & Lipton, D., SIAM J Applied Math 48:1073 (1988)). Methods commonly employed to determine identity or similarity between two sequences include, but are not limited to, those disclosed in Guide to

-21-

Huge Computers, Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carillo, H. & Lipton, D., SIAM J Applied Math 48:1073 (1988). Methods to determine identity and similarity are codified in computer programs. Preferred computer program methods to determine identity and similarity between two sequences include, but are not limited to, GCG program package (Devereux, J., et al., Nucleic Acids Research 12(I):387 (1984)), BLASTP, BLASTN, FASTA (Atschul, S.F., et al., J Molec Biol 215:403 (1990)).

Therefore, as used herein, the term "identity" represents a comparison between a test and a reference polypeptide or polynucleotide. For example, a test polypeptide may be defined as any polypeptide that is 90% or more identical to a reference polypeptide.

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As used herein, the term at least "90% identical to" refers to percent identities from 90 to 99.99 relative to a reference polypeptide. Identity at a level of 90% or more is indicative of the fact that, assuming for exemplification purposes a test and reference polynucleotide length of 100 amino acids are compared. No more than 10% (i.e., 10 out of 100) amino acids in the test polypeptide differs from that of the reference polypeptides. Similar comparisons may be made between a test and reference polynucleotides. Such differences may be represented as point mutations randomly distributed over the entire length of an amino acid sequence or they may be clustered in one or more locations of varying length up to the maximum allowable, e.g. 10/100 amino acid difference (approximately 90% identity). Differences are defined as nucleic acid or amino acid substitutions, or deletions.

As used herein, AMBER is a force field well known in the arts and designed for the study of proteins and nucleic acids as defined in Weiner et al. J. Comput. Chem. (1986) 7:230-252, where a modified AMBER (version 3.3) force field is a fully vectorized version of AMBER (version

3.0) with coordinate coupling, intra/inter decomposition, and the option to include the polarization energy as part of the total energy. AMBER is available in commercially available molecular modeling programs such as, but not limited to, Macromodel (Columbia University).

As used herein, ECEPP (Empirical Conformational Energies of Peptides Program) is a force field well know in the arts (US Patent No. 5,910,478; 5,846,763). ECEPP/3 refers to version 3 of this well known force field.

As used herein, QSAR refers to structure-activity relationship.

10 As used herein, vdw refers to van der Waals.

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As used herein, RMSD refers to root mean-squared deviation.

As used herein, medical history refers to the parameters and data typically obtained by a physician when examining a subject or other such professional when examining other mammals, and includes such information as prior diseases, age, weight, height, sex and other information. For purposes, the subjects that serve as the source of the samples from which nucleic acids encoding polymorphisms are isolated, include animals, plants, pathogens and any organism that has nucleic acid that exhibits polymorphism. In this context medical history refers to information pertinent to the particular organism.

As used herein, subject history, refers to data such as locale in which the subject was born, raised or resident or visited, and parental history and other such information.

As used herein, a drug is an agent that binds to or interacts with a targeted protein. For purposes, a therapeutic agent is a drug.

B. Computer-based methods of drug design based on genetic polymorphisms

Methods for computer-based drug design based on genetic polymorphisms are provided. The methods includes the steps of obtaining one or more, preferably two or more, amino acid sequences of a target

-23-

protein that is the product of a gene exhibiting genetic polymorphisms; generating 3-dimensional (3-D) protein structural variant models of all or a portion of the protein from the sequences; and based upon the structures of the 3-D models, designing drug candidates or modifying existing drugs based on the predicted intermolecular interactions of the drug candidates or modified drugs with the structural variants or portions thereof by computationally docking drug molecules with the target protein models; and then, optionally energetically refining the docked complexes; determining the binding interactions between the drug or potential new drug candidate molecules and the models by calculating the free energy of binding of the docked complexes and decomposing the total free energy of binding based on interacting residues in the protein active site or sites deemed important for protein activity.

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A variety of methods that include these steps are provided. Such methods have particularl application, for example, in predicting patient responses. As noted, patients exhibit variable responses to drugs. For some patients a drug may be very beneficial and achieve a desired response; whereas for other patients, with the same disorder, the same drug will have little or no effect. It is known that individuals as well as groups of individuals exhibit a variety of genetic polymorphisms. As described herein, the presence or absence of such polymorphisms can be correlated with the variability of patient responses to drugs.

It is shown herein that by understanding how genetic polymorphisms affect 3-D protein structure of a drug target, for example, it is possible to ascertain the interaction of a particular drug with the target in a particular patient or groups of patients. Based upon this interaction, the outcome can be predicted. It will be possible to determine whether a patient will benefit from a drug or be at risk for a particular side effect. It is possible to predict these responses before exposure to the drug. These

methods also permit rational design of drugs that can treat various populations or ultimately even individuals. These differences and effects can also be taken into account to design drugs that are not dependent upon a particular polymorphism.

Hence, the knowledge derived from understanding the effects of genetic polymorphisms can be used to develop and apply therapeutics more effectively, make clinical trials more successful, for example, by permitting selection of test subjects with the same polymorphism or with polymorphisms for which the drug is designed to interact effectively.

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It is shown herein that it is advantageous to use 3-D molecular structures in drug design rather than to consider primary sequence alone. For example, most drugs target proteins either in the afflicted organism or in a pathogen. Disease, drug action and toxicity are all manifested at the protein level. Although the nucleotide sequences of genetic polymorphisms might appear to be quite different, the resulting protein targets may have similar shapes and, therefore, the protein biological function might be the same. Conversely, although genetic polymorphism sequences might appear similar, the resulting proteins may have critical differences in their 3-D structures that greatly affect biological activity. Thus, use of 3-D protein structure models in such methods provide advantages not heretofor realized. Methods for generating 3-D structures are known to those of skill in the art and are also provided herein.

Once the protein target structural models have been selected, structure-based drug discovery methodologies, for example, computational screening or docking programs and methods (e.g., DOCK (available from University of Ca, San Francisco; and AUTODOCK available from Scripps Research Institute, La Jolla), are used to design biologically-active compounds based on the 3-D structures of the biomolecular receptors. Using these methods, drug designers can identify and

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computationally rank the various potential clinical drug candidates for maximum efficacy, thereby performing drug discovery in silico and avoiding the tedious time and expense associated with in vitro drug discovery methods.

In addition to drug design applications, the information derived from studying the structures of biological targets can be used to understand and predict biological responses in patients, such as efficacy, toxicity, drug resistance and other pharmacological effects. Since human clinical trials may cost upwards of \$100-300 million, it is desirable to predict the 10 outcome to the greatest extent possible for each prospective drug candidate so that the best prospective drug candidates are advanced to clinical trials. As described below, methods are provided herein for selecting populations for clinical trials.

Methods for obtaining amino acid sequences of a target 1. protein

Any protein or gene or encoded mRNA that exhibits polymorphisms, herein referred to as the target protein, in structure is contemplated for use herein and for generating the databases as provided The target protein is a protein, polypeptide, or oligopeptide that includes, but is not limited to, receptors, enzymes, hormones, prions, or any such compound with which drugs or other ligands, such as small molecules, peptide agonists, peptide antagonists, other proteins, nucleic acids and other biomacromolecules, interact to bring about a biological response. These target proteins occur in any organism, including plants and animals, eukaryotes and prokaryotes, including pathogens, such as protozoans, parasites, viruses, includind DNA and retroviruses, and bacteria. The protein or gene can be one expressed in the organism, such as molecule targeted for drug interaction, or one expressed in a pathogen.

-26-

The target gene is one that exhibits polymorphisms (i.e., sequence variations among a population) and the target protein is the product of a gene exhibiting genetic polymorphisms, or sequence variations, as described herein. Any gene or protein that exhibits polymorphisms is contemplated herein. In particular, genes that encode proteins, polypeptides, or oligopeptides that are targets for drug interaction are contemplated herein. The genetic polymorphisms can occur in the genes of pathogens (e.g. viruses, bacteriae, and fungi), parasites, plants, animals, and humans. As such, the sequence a target protein can be obtained by the isolation and analysis of the gene or gene product in samples taken from pathogens, parasites, plants, animals, and humans, most preferably from humans.

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The genes or proteins may be isolated from any source, such as animal or plant specimens, or the sequences obtained from any source, including known databases. If starting with gene sequences that include single or multiple nucleotide polymorphisms, the amino acid sequences of the translated proteins can be determined. Protein isolation and sequencing methods are well known to those of skill in the art. Alternatively, samples of the target protein can be obtained and sequenced directly from specimens. Multiple sequence analyses can be performed to determine the exact amino acid variations or mutations resulting from the genetic polymorphisms.

Amino acid sequences of target proteins can also be obtained from data banks and databases (e.g. GenBank, Swiss Prot, PIR) and from publications and other sources in which numerous polymorphisms have been identified and mapped. Samples may be obtained from, for example blood and tissue banks, nucleic acid isolated, genes selected or identified and polymorphims can be mapped from such samples.

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2. Generation of 3-D protein structural variant models

After the amino acid sequences of target proteins are obtained via the means described in section 1, the 3-D structural models of the sequences of native proteins or of the protein structural variants are then determined. They can be determined through experimental methods, such as x-ray crystallography and NMR, and from structure databases, such as the Protein Databank (PDB). Moreover, 3-D structural models can be determined by using any of a number of well known techniques for predicting protein structures from primary sequences (e.g. SYBYL (Tripos Associated, St. Louis, Mo.), de novo protein structure design programs (e.g. MODELER (MSI, Inc., San Diego, CA) and MOE (Chemical Computing Group, Montreal Canada) and ab initio methods, see, e.g., U.S. Patent Nos. 5,331,573, 5,579,250 and 5,612,895), homology modeling, and ab initio computational analysis. Homology modeling, structure determination based upon x-ray crystallographic structures, and ab initio techniques and combinations of these methods are among those preferred herein.

a. Homology Modeling

Homology modeling is based on the relationship between protein evolutionary origin, function and folding patterns. Proteins of related origin and function have conserved sequences and structural features among the members of a homologous family. Using these relationships, a three-dimensional structural model for a protein of unknown structure can be constructed by using composite parts of related proteins in the same family. Where only the primary amino acid sequence of a target protein is known, the sequence can be compared to the sequences of related proteins with known structures (reference proteins), and a model can be built by incorporating the structural attributes of the reference protein together with the sequence of the target protein.

Sequence homology calculations generally require: the amino acid sequence of the target protein; a high resolution structure for at least one, but preferably more, related reference proteins; and any other related amino acid sequences. The reference proteins include structures which are similar to the target protein, either by sequence, fold, function, or which are polymorphisms of the target protein. The more related protein structures and sequences that are available or determined, the more reliable the technique will be at providing an accurate model.

In constructing a protein model using homology modeling, sequence alignment is performed between the target sequence and any known structures within the protein family. Sequence alignment requires determining the similarity between protein sequences by maximizing the number of matches between the sequences while introducing the minimum number of insertions and deletions. Sequence alignment algorithms are well known in the art, and standard gap penalties (*i.e.*, programs that automatically introduce gaps to maximize alignment and then adjust the percentage of identity by applying penalties for gap number and gap length) and other parameters can be selected by the skilled artisan. Additionally, the 3-D structures of the known reference proteins, preferably, are aligned to give the best overall fit for the proteins in the family. This provides indication of structurally-conserved regions, such as regions of the proteins that do not contain insertions or deletions, among the reference structures.

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Once the sequences are aligned and the structurally-conserved regions are identified, the coordinates of the reference proteins can be used to construct a 3-D model of the target structure. Coordinates from the protein backbone of the reference proteins are then used to construct the backbone framework for the target protein structure. Side chains can be constructed, for example, by using side chain coordinates from the

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reference proteins, searching from a database to obtain side chain conformations that fit in with the existing structural framework or by generating side chains ab initio to establish energetically favorable side chain conformations.

The non-conserved regions of the unknown protein can be constructed, for example, using database searching. A database of known protein structures (e.g., PDB) can be searched to identify variable regions in other proteins that have a high degree of sequence similarity to the target sequence and that fit onto the existing structural framework of the 10 protein model. Algorithms for performing sequence similarity matching and homology model building are well known in the art and are available commercially (available from Molecular Simulations, Inc., Tripos, Inc. and from numerous academic sources).

The variable regions can also be modeled by fitting the target sequence to a peptide backbone generated by varying phi and psi angles (e.g., by calculating Ramachandran or Balasubramanian plots, see, Balasubramanian (1974) "New type of representation for Mapping Chain Folding in Protein Molecules," Nature 266:856-857) or Balaji plots, see, U.S. Patent Nos. 5,331,573, 5,579,250 and 5,612,895) of the amino acids to give a loop structure that can be integrated into the model structure based on a sterically and energetically reasonable fit (Figure 1).

In a Balasubramanian plot, the peptide is depicted as a series of different vertical lines, each having solid dots and open circles aligned with the corresponding ϕ , ψ angle values on the vertical axis, and where each line corresponds to the particular number of the residue having the plotted ϕ , ψ angles as indicated on a horizontal axis. In the Balaji plot, the values of the ϕ , ψ angles are shown as the base and tip of a vertical wedge (assuming a vertical angular axis), respectively, with a separate wedge being horizontally positioned on the plot as a function of the

-30-

residue number of the ϕ , ψ angles plotted. The Balaji plot replaces the solid dots and open circles of the Balasubramanian Plot with the base of a wedge and the tip of a wedge, respectively; and further replaces the vertical line joining the dots and open circles of the Balasubramanian plot with the body of the wedge.

b. Ab initio generation of 3-D structures

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Alternatively, ab initio methods can be used in combination with an existing partial homologous structure to generate unresolved portions of the target structure. Such methods are described, for example, in U.S. Patent Nos. 5,331,573, 5,579,250 and 5,612,895, which as all patents, applications and publications referenced herein, are each incorporated in their entirety. These methods involve: simulating a real-size primary structure of a polypeptide in a solvent box, i.e., an aqueous environment; shrinking the size of the peptide isobarically and isothermally; and expanding the peptide to its real size in selected time periods, while measuring the energy state and coordinates, i.e., the bonds, angles and torsions of the expanding molecule. As the peptide expands to its full size, it assumes a stable tertiary structure. In most cases, due to the manner in which the expansion occurs, this tertiary structure will be either the most probable structure (i.e., it will represent a global minimum for the structure) or one of the most probable structures. The energy equations used to perform the ab initio simulation are based on the potential energy of the simulated molecule as described using molecular mechanics.

Once a model is built, it can be refined using energy minimization, molecular dynamics calculations, or simulated annealing as described herein. The steric and energetic quality of the structural models is then evaluated by analyzing the structural attributes of the model, such as phi and psi angles (e.g., by calculating Ramachandran or Balasubramanian or

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Balaji plots), or the energetics of the model, such as by calculating energy per residue or strain energy. If the overall quality of the model is not satisfactory, further iterative energy refinement can be performed until the model is considered to be acceptable (*i.e.*, $e_{av} < 1.5$, see below).

A preferred method for generating and refining the structural variant models is illustrated in **FIG. 1**. First, at block 100 of FIG. 1, protein sequence information, derived genetic polymorphisms, is obtained from the methods described earlier. At block 102, the protein is assigned to a protein superfamily in order to identify related proteins to be used as templates to construct a 3-D model of the protein. If the superfamily is not known, sequence analysis or structural similarity searches can be performed to identify related proteins for use as templates in homology modeling studies, as described herein, as indicated at block 104.

Once the conserved regions of the model are assembled, ab initio loop prediction (Dudek et al. (1998) J. Comp. Chem. 19:548-573) indicated at 106A or ab initio secondary structure generation techniques of block 106B, techniques in which the alignments are adjusted using information on the secondary structure, functional residues, and disulfide bonds as described herein, can be used to complete the model (e.g. U.S. Patents Nos. 5,331,573; 5,579,250; and 5,612,895). This model, complete with loops, is then subjected to refinement procedures (block 110) based on molecular mechanics, molecular dynamics, and simulated annealing methods. Energetic refinement of the structure can be accomplished by performing molecular mechanics calculations using, for example, an ECEPP type forcefield (Dudek et al. (1998) J. Comp. Chem. 19:548-573) or through molecular dynamics simulations using, for example, a modified AMBER type forcefield (Ramnarayan et al. (1990) J. Chem. Phys. 92:7057-7076. As known to those of skill in the art a modified AMBER (version 3.3) force field is a fully vectorized version of

-32-

AMBER (3.0) with coordinate coupling, intra/inter decomposition, and the option to include the polarization energy as part of the total energy (see, e.g., Weiner et al. (1986) J. Comp. Chem. 7:230-252). If necessary, the 3-D structures can be dynamically refined, for example, by using a simulated annealing protocol (e.g.,, 100 ps equilibration, 500 ps dynamics, up to 1000°K, 1 fs data collection).

The refinement process step 110 is used to offset problems that may arise when homology models are not built carefully or when they are built using fully automated methods. Problems that may arise include chain breaks (e.g. consecutive C^a atoms are farther apart than the optimum distance of 3.7 to 3.9 Å); distorted geometry (e.g. bond lengths and bond angles are too far from their optimal values); cis-peptide bonds (e.g., incorrect isomerization of the peptide backbone in non-proline residues when it is not required); disallowed backbone and side-chain conformations (e.g., dihedral angles do not satisfy the Ramachandran plot (see, Balasubramanian (1974) Nature 266:856-857) criteria for a fully favorable protein structure conformation); and misfolded loops (e.g. nonhomologous loops are generated in unnatural conformations). The refinement procedure 110 removes distortions of covalent geometry by using energetic methdods, converts disallowed backbone and side-chain conformations into allowed ones using simulated annealing methods, conserves protein core structure and secondary structural elements built by homology, and rebuilds unnatural loop constructions (Dudek et al. (1998) J. Comp. Chem. 19:548-573).

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For quality control (block 112), the protein structural characteristics, for example, stereochemistry (e.g.,, phi/psi and side chain angles), energetics (e.g.,, strain energy), packing profile (e.g.,, packing factor per residue) and hydrophobic packing are evaluated and required to meet acceptable criteria before the structures are used in further studies

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or inputted into a structural polymorphism database. Quality control using strain energies entails computing normalized residue energies (NREs) based on the equation:

$$e_i = [E(i,X) - E_{AV}(X)] / E_{SD}(X)$$
, where

E(i,X) is the energy of interactions of amino acid X in position i with protein environment and solvent;

 $E_{AV}(X)$, $E_{SD}(X)$ is the average residue energies and their standard deviations calculated for 20 amino acids in more than 100 high-quality crystal structures; and

NREs characterize how favorable the interactions of each residue are within the protein environment (Majorov and Abagyan, (1998) Folding & Design 3:259).

The average NRE characterizes the overall quality of a protein structure and is defined as:

 $e_{av} = (1/N) \Sigma_i e_i$, where

 $e_{av} \le 0.5$ denotes high-resolution X-ray crystal structures;

 $e_{av} \leq 1.0$ denotes good as NMR and theoretical models; and

 $e_{av} \ge 1.5$ denotes structures that require further refinement.

After the quality of structure is determined at block 112, the model is checked at block 114 to determine if it is satisfactory. If the overall quality of the model is not satisfactory, a "No" outcome at block 116, then remedial action is undertaken to fix problems at block 118, including further iterative energy refinement (block 110), and repeated checking (block 114). The refinement and evaluation is repeated until the model is considered to be acceptable, a "Yes" outcome at block 120, whereupon structural and/or physical properties (e.g. energetics and phi/psi angles) are calculated at block 122A and clinical data (if available) is obtained at block 122B. The model is then inputted into a structural polymorphism database at block 124.

-34-

FIG. 2 shows an exemplary method for generating structural variant models derived from genetic polymorphisms and using them in structure-based drug design studies. At the block numbered 200, patient data is acquired for a gene that exhibits genetic polymorphisms. Protein sequence information is then derived, at block 202. A check is made for determination of the 3-D structure of the native protein. If the 3-D structure has been determined, a "Yes" outcome at block 206, then a multiple sequence analysis is performed at block 208 to determine the exact amino acid variations for the structure. If the 3-D structure has not been determined, a "No" outcome at block 210, then the structure is determined using physiochemical methods at block 212.

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Next, at block 214, the 3-D structural models for all variants are generated. A refinement process is then completed at block 216 for the structural models. As noted above in connection with FIG. 1, the process involves subjecting each model, complete with loops, to refinement procedures based on molecular mechanics, molecular dynamics, and simulated annealing methods. As before, the energetic refinement of the structure can be accomplished by performing molecular mechanics calculations using an ECEPP type forcefield (Dudek et al. (1998) J. Comp. Chem. 19:548-573), or through molecular dynamics simulations using, for example, a modified AMBER type forcefield (Ramnarayan et al. (1990) J. Chem. Phys. 92:7057-7076), where a modified AMBER (version 3.3) force field is a fully vectorized version of AMBER (3.0) with coordinate coupling, intra/inter decomposition, and the option to include the polarization energy as part of the total energy (Weiner et al. (1986), J. Comp. Chem. 7:230-252). If necessary, the 3-D structures can be dynamically refined, for example, by using a simulated annealing protocol (e.g.,, 100 ps equilibration, 500 ps dynamics, up to 1000°K, 1 fs data collection).

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At block 218, a quality evaluation is performed for all the models. As described in connection with the quality evaluation process in Fig. 1, the evaluation at block 218 involves evaluating the protein structural characteristics, for example, stereochemistry (e.g., phi/psi and side chain angles), energetics (e.g., strain energy), packing profile (e.g., packing factor per residue) and hydrophobic packing, which must meet acceptable criteria before the structures are used in further studies or inputted into a structural polymorphism database.

After the model quality is determined, at block 220 the models are checked to determine if they are satisfactory for further use. If a model is not satisfactory, a "No" outcome at block 222, then the problems are identified and solved with remedial action at block 224. The remedial action may include further iterative energy refinement at block 216 and repeated checks of model quality at block 218. Once the models are satisfactory, a "Yes" outcome at block 226, structure-based drug design methods are applied at block 228 to identify potential new drugs that bind to the structural variant models. The drug design methods are described further below.

FIG. 3 shows another exemplary and alternative method for generating structural variant models derived from genetic polymorphisms and using them in structure-based drug design studies. The process of FIG. 3 is similar to the process of FIG. 2 from the initial process at block 300 of acquiring patient data for a gene that exhibits genetic polymorphisms through the process of obtaining models that are satisfactory (a "Yes" outcome at block 326). Thus, block numbers in FIG. 3 from 300 through 326 that correspond to FIG. 2 blocks numbered from 200 thorough 226 refer to similar operations. Unlike FIG. 2, however, the process illustrated in FIG. 3 then involves docking operations.

-36-

At block 328, once the models are determined to be satisfactory, drug molecules are docked with the structural variant models. Next, at block 330, the free energy of binding is evaluated with the potential drugs under study for each structural variant model. At block 332, the total free energy of binding is decomposed, based on the interacting residue in the protein active site. Lastly, at block 334, the free energy of binding is correlated with patient data, if the data is available. Thus, the 3-D structural data is employed in drug design. Details of using such structural data in drug design are described further below.

c. Crystal structures

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The crystal structure of any protein can be determined empirically and the resulting coordinates used as the basis for determing structures of variants. Such structures are often known (see, e.g., Kohlstaedt et al. (1992) Science 256:1773-1790 for a crystal structure of HIV-1 RT bound to a ligand).

3. Use of 3-D structural variant models in drug design

The structural differences in protein structural variants that arise due to genetic polymorphisms can have profound effects on biological activity. Because of the structural differences among the variants, they may have different physical or reactive properties and therefore may exhibit different biological activities. These differences may include, for example, different responses to a given drug, so that a drug which works well in a patient with one particular genetic polymorphism may not work as well in another patient exhibiting a different polymorphism.

The 3-D molecular structures of drug targets derived from genetic polymorphisms can be used in structure-based drug design studies to greatly advance the development of new pharmaceuticals. Relational databases of these 3-D structures that are derived from samplings of genetic polymorphisms over a patient population or a cross-section of the

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population can be used to design potential drugs in order to optimize effectiveness for the particular population.

The structures and databases described herein can provide information that is useful, for example, in designing a drug that is effective in the greatest percentage of the population. It is desirable that a given drug is effective in the largest percentage of the population, since such a drug is likely to have the greatest clinical utility and thus the greatest commercial value. A drug with superior performance properties is sometimes referred to as a "best in class" drug and is highly prized by pharmaceutical companies since this heralds market leadership and the likelihood of commercial success. The databases and methods described herein can be used to determine 3-D protein structures for drug targets that are associated with particular genetic polymorphisms and to use the structures in drug design studies for design and optimization of candidate drugs that exhibit activity over the broadest patient population.

Genetic polymorphisms may result in target protein structural variants in which drug efficacy correlates with specific populations or subpopulations. In some cases, it might be desirable to target drug design or drug therapy toward a specific patient population, such as a particular race, gender, or age group, affected by a certain disease or condition or toward those having a specific genetic polymorphism. The information derived from comparing the 3-D structural variants arising from different genetic polymorphisms may be useful for understanding why drugs are active or inactive in different subpopulations, or for assisting in developing new drugs to maximize efficacy across specific populations.

-38-

a. Selection of relevant structural variants

The structural variant models in the structural polymorphism database provided herein can be used to design new drugs or to select a drug therapy that would be appropriate for a patient exhibiting a particular genetic polymorphism. As it may not be possible for a drug to work equally well for all polymorphisms, and thus all patients, representative structural variants can be selected for use in drug design studies in order to maximize biological activity based on genetic polymorphisms.

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In some cases, structural variants are analyzed to determine the common structural features that are conserved through the selected models. These conserved features are used as a basis for drug design. In some cases, the structural variant corresponding to the genetic polymorphism occurring most commonly in a population can be selected for use in identifying drugs that would be effective in the greatest percentage of the population. Optionally, structural variants corresponding to a relevant subpopulation, such as a particular gender, age, race, or other characteristic, can be selected for use in designing drugs that are active in that subpopulation. In other cases, individual structural variant models can be selected for use in designing drugs that are specifically active against one target in one individual arising from a particular genetic polymorphism. Additionally, model structures that represent variants derived from patients that receive a specific treatment regimen or exhibit a particular clinical response (e.g. drug resistance) to a given drug are used as bases for drug design.

The relevant structural variants may be identified using the structural analysis tools described herein, optionally in combination with database and statistical analysis tools that permit a complete analysis and comparison of the molecular structures and properties of the structural

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variants. The structural variants selected based on the criteria including, but not limited to, those listed above are used in drug design.

b. Drug design

Once the protein target structural models have been selected, structure-based drug discovery methodologies, for example, computational screening or docking (e.g., DOCK (available from University of Ca, San Francisco; and AUTODOCK available from Scripps Research Institute, La Jolla and others referenced herein or known to those of skill in the art), can then be used to design biologically-active compounds based on the 3-D structures of the biomolecular receptors.

Using these methods, drug designers can identify and computationally rank various potential clinical drug candidates for maximum efficacy, thus cutting the time and expense associated with drug discovery. The preferred design of drug candidates or the modification of existing drugs is based on the intermolecular interactions between the drug candidate or modified drugs and the selected structural variants predicted by computationally docking drug molecules with the target protein models; energetically refining the docked complexes; determining the binding interactions between the drug or potential new drug candidate molecules and the models by calculating the free energy of binding of the docked complexes and decomposing the total free energy of binding based on interacting residues in the protein active site or sites deemed important for protein activity.

c. Computational docking

Methods for using the structural variant models to design potential new drugs or to aid in the selection of a drug therapy based on the interactions of selected small molecules with the particular variants are provided. Structure-based drug design experiments, such as computational screening or docking studies, calculation of binding

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energies or analysis of steric, electrostatic or hydrophobic properties of the resulting structural variant models, can be performed on selected structural variant models to aid in the understanding of observed biological activities or to determine new potential drug candidates to bind to the particular target.

In a typical computational docking protocol, the active site, or sites deemed important for protein activity, of the protein model is defined. A molecular database, such as the Available Chemicals Directory (ACD) or any database of molecules, is screened for molecules that complement the protein model. Solvation parameters are factored in (see, e.g., 10 Shoichet et al. (1999) PROTEINS: Structure, Function, and Genetics 34:4-16). In these computational docking studies, drugs or drug candidates are fitted to the structural variant models based on complementary interactions (e.g., steric, hydrophobic, or electrostatic interactions). Methods for performing such studies are well known and software tools for performing the calculations are widely available (M. Lambert, "Docking Conformationally Flexible Molecules into Protein Binding Sites" in Practical Application of Computer-Aided Drug Design, Charifson, Ed., Marcel Dekker, NY, pp. 243-303; Kurtz (1992) Science 257:1078-1082; Kuntz et al. (1982) J. Mol. Biol. 161:269-288; Stewart et al. (1992) Med. Chem. Res. 1:439-443; Shoichet et al. (1993) Science 259:1445-1450;

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New potential drug candidates can be designed by identifying potential small molecule drugs that can bind to a particular structural variant. This is accomplished, for example, by methods including, but are not limited to, methods for electronic screening of small molecule databases as described herein, methods involving modifying the functional groups of existing drugs in silico, methods of de novo ligand design. Methods for computationally desiging drugs are known to those

Shoichet et al. (1991) J. Mol. Biol. 221:327-346).

-41-

of skill in the art and include, but are not limited to, DOCK (Kuntz et al. (1982) "A Geometric Approach to Macromolecule-Ligand Interactions", J. Mol. Biol., 161:269-288; available from University of Ca, San Francisco); and AUTODOCK (see, Goodsell et al. (1990) "Automated Docking of Substrates to Proteins by Simulated Annealing", Proteins: Structure, Function, and Genetics, 8, pp. 195-202; available from Scripps Research Institute, La Jolla); GRID (Oxford University, Oxford, UK); CAVEAT (UC Berkeley, Ca), LEGEND (Molecular Simulations, Inc., San Diego, CA); LUDI (Molecular Simulations, Inc., San Diego, CA); HOOK (Molecular 10 Simulations, Inc., San Diego, CA); CLIX (CSIRO, Australia); GROW (Upjohn Laboratories, Kalamazoo); others including HINT, LUDI, NEWLEAD, HOOK, PRO-LIGAND and CONCERTS (see, M. Murcko, "An Introduction to De Novo Ligand Design" in Practical Application of Computer-Aided Drug Design, Charifson, Ed., Marcel Dekker, NY, pp 305-354), methods based on QSAR (quantitative structure-activity 15 relationships, QSAR and Drug Design: New Developments and Applications, Fugita, Ed., (1995) Elsevier, pp 3-81; 3D QSAR in Drug Design, Kubinyi, Ed., (1993) Escom, Leiden), and other methods known to those of skill in the art for determining molecules that have optimal binding interactions with a selected target. 20

The docked complexes, if needed, are further refined energetically to optimize geometries within the binding site and to select the best structure from a set of possible structures, using molecular mechanics, molecular dynamics, and simulated annealing techniques, including those described herein and others that are known to those skilled in the art.

d. Free energy of binding studies

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After the computational docking step, the free energy of binding of the docked complex is calculated, and the total free energy of binding is decomposed based on the interacting residues in the protein active site or

sites deemed improtant for protein activity. Analyses of the binding energies are needed to identity drug candidates. If need or desired, the free energy of binding of different drugs or potential drugs to each structural variant model can be calculated by substracting the free energy of the non-interacting protein and drug from the free energy of the protein-drug complex. The total free energy of binding is decomposed into its various thermodynamic components, e.g. enthalpic and entropic components, based on the interacting residues in the protein active site in a solvated model to characterize the structural and thermodynamic features in the mode of drug binding and to determine the contribution of the solvent] (see, e.g., Wang et al. (1996) J. Am. Chem. Soc. 118:995-1001; Wang *et al.* (1995) *J. Mol. Biol. 253*:473-492; Ortiz *et al.* (1995) J. Med. Chem. 38:2681-2691, which describes a computational method for deducing QSARs from ligand-macromolecule complexes). Following the computational drug design protocol described herein, any potential new drugs that are identified can be synthesized in, for example, industry or academia, and subjected to further biological testing, such as in vitro studies or pre-clinical and clinical in vivo testing.

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Based on the predicted intermolecular interactions of the drugs or modified drugs with the structural variant models from binding studies, potential drug candidates that are specific for a protein with a selected polymorphism or that specifically interact with all proteins exhibiting the polymorphism can be identified.

It is also possible to individualize drug design or drug therapy by determining the structural variants associated with a particular patient and then designing or screening drugs or potential drugs to maximize efficacy in that subject or in a subpopulation that exhibits the same genetic polymorphism. The variants may also be used to track polymorphic variations in infectious organisms, such as viruses. For example, the

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human immunodeficiency viruses (HIVs) reverse transcriptase and protease have served as drug targets (see, Erickson et al. (1996) Ann. Rev. Pharmacol. Toxicol 36:545-571); their three-dimensional structures are known (see, e.g., Nanni et al. (1993) Perspectives in Drug Discovery and Design 1:129-150; Kroeger et al. (1997) Protein Eng. 10:1379-1383). The clinical emergence of drug-resistant variants of these viruses has limited the long-term effectiveness of drugs targeted against these enzymes.

As noted, these enzymatic proteins in order to preserve function must exhibit conserved 3-D structures. The methods herein permit design of drugs specific for the conserved regions of the 3-D structures. They also permit selection of drug regimens based upon the alleles expressed. Hence, methods for designing HIV enzyme-specific drugs are provided. Flow charts illustrating exemplary alternative embodiments using protein 3-D structures derived from genetic polymorphisms in structure-based drug design studies are provided (see, Figs. 2 and 3). In the flow charts depicted in these figures, the drug design includes structure-based drug design methods (see, Figure 2) and computational docking of drugs with structural variants, evaluation of the binding energy of the docked complexes, and correlation of the binding energy with patient data such as age, gender, race, drug treatment history, and any other pertinent information that is available (see, Figure 3). The data generated by this computer-based method can be stored in a database, such as, for example, in a relational database. The resulting database can be screened using searching tools to select potential drugs and therapeutic agents that bind to or exhibit biological responses towards target proteins.

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C. Applications of computer-based methods

As discussed above, the computer-based methods provided herein include some or all of the steps of obtaining one or more, preferably two or more, amino acid sequences of a target protein that is the product of a gene exhibiting genetic polymorphisms; generating 3-dimensional (3-D) protein structural variant models from the sequences; and based upon the structures of the 3-D models, designing drug candidates or modifying existing drugs based on the predicted intermolecular interactions of the drug candidates or modified drugs with the structural variants by computationally docking drug molecules with the target protein models; energetically refining the docked complexes; determining the binding interactions between the drug or potential new drug candidate molecules and the models by calculating the free energy of binding of the docked complexes and decomposing the total free energy of binding based on interacting residues in the protein active site or sites deemed important for protein activity. There are numerous applications of these methods, which include structure-based drug design and drug testing; selection of clinically relevant populations for drug testing and other such methods.

1. Genetic polymorphisms and structure-based drug design

As noted above, structure-based drug design is an increasingly useful methodology that has made a great impact in the design of biologically active lead compounds. Drug designers can design and screen potential new drugs via computational methods, such as docking or binding studies, before actually beginning patient testing. The drugs designed by such methods, and also those identified by traditional methods of drug discovery, are then tested in clinical trials. Among those that show efficacy for a particular indication and low toxicity ultimately are approved for use. It is found, however, that not all patients with a

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particular indication respond uniformly to the drugs. The drug may not be efficacious or side-effects may be pronounced.

The methods provided herein, represent a further advance in the use of rational drug design methods. As described herein, polymorphic variation has an effect upon the 3-D structure of encoded proteins. As a result, drugs interact with variants differently, leading to differential responses in the population as a whole. A new approach to drug design and testing is provided herein. This methods involves identifying polymorphisms and determining 3-D resulting structures, which are then used in methods, including, computational drug design, in the selection of patient populations, in designing treatment protocols and in other applications.

2. Drug resistance

Methods for understanding and overcoming drug resistances by using 3-D protein model structures resulting from multiple genetic polymorphisms or mutations in an infectious agents, such as viruses, bacterial and other pathogenic agents are provided. Also provided are methods that for using this information in drug design studies.

In the case of infectious organisms or other replicating or mutating agents, such as flu, HIV, rhinovirus or biological warfare agents, some polymorphisms or mutations may arise over time which convey resistance or susceptibility to specific drug therapy, for example, by altering the drug target structure or physical properties so that a specific drug or therapy, such as an antibiotic or vaccine, may no longer be able to bind to or otherwise interact with the target protein to exert its desired biological effect. For certain infectious agents, such as HIV, genetic polymorphisms in certain genes give rise to drug resistance as the virus mutates (see, e.g., Erickson et al. (1996) Annu Rev. Pharmacol. Toxicol. 36:545-571).

-46-

Where drug resistance that arises from mutations or polymorphisms is observed, the methods described herein can be used to develop new drugs that overcome the resistance. For example, once drug resistance is observed, the structure associated with the resistant polymorphism can be determined and used in further drug design studies to suggest new drugs or modifications to the existing drug that will restore biological activity by targeting different mutants or that will target multiple mutants simultaneously.

The model structures can also be used to correlate drug resistance in infectious diseases with the structural variants derived from genetic polymorphisms. Here, the 3-D structure of the virus or other drug target is determined for the particular variant model against which the drug was effective. When drug resistance arises due to a genetic polymorphism, a model for the structure variant associated with the resistant organism can be generated, and a new drug can be designed or modifications can be made to the existing drug to overcome the resistance.

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For example, samples of the mutating organism can be obtained over time and structural models for the resulting proteins can be generated. These models can then be used to design new drug therapies that are active against the mutated organism. Multiple drug resistant structures can be analyzed to obtain an average structure or to identify common structural features in order to design new drugs that have the broadest spectrum of activity against multiple mutations.

Such structural information is useful in designing effective drug therapies to overcome resistance or to develop drugs that are effective over a range of genetic polymorphisms and thus work for the maximum number of patients.

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3. Identification of conserved structural features or pharmacophores

If common structural features are observed over a range of protein targets that are derived from genetic polymorphisms, these common features may be used to design a drug that is effective with a variety of genetic polymorphisms and thus many patients. The retention of certain common structural features over a large number of genetic polymorphisms suggests that those features may not be mutatable because the conserved structure may be essential to protein function,

10 e.g., to the viability of an infectious organism or virus. Such conserved structural elements are prime targets for structure-based drug design, e.g., anti-infective or antibiotic drug design, and can lead to highly effective therapies.

The common structural features can serve as a basis for structure-based drug design, for example, by serving as a scaffold for building a receptor model into which potential drug candidates can be docked or as a pharmacophore query for screening a library of physical or virtual chemical or biochemical molecules to identify compounds that match the pharmacophore template and, thus, are potential drug candidates.

Analysis of 3-D protein structural variants derived from genetic polymorphisms to identify the common structural features over a large number of structural variants can aid in the design of drugs that are active over a broad range of genetic polymorphisms, such as in a large number of patients or against drug resistant targets.

In comparing sets of related protein structures, such as those with the same biological function or those resulting from genetic polymorphisms, certain parts of the structural framework are often found to be conserved, while other parts vary among the proteins. Mutations that occur in the conserved regions of the structure can have significant effects biological activity. For example, in viruses, the conserved features

can be essential to protein function and, thus, to the viability of the infectious organism or virus. Identifying the conserved structural features over a range of structures often gives insight into which structural features are necessary for biological activity and are therefore non-mutatable. By analyzing a number of structural variants derived from genetic polymorphisms that exhibit drug resistance, it is possible to identify or design drugs that interact best with the common structural features in all of the variants. Using these features in structure-based drug design studies leads to the identification of drugs that retain biological activity despite multiple mutations, or polymorphisms, and could help to overcome the problem of drug resistance.

In certain preferred embodiments, new potential drug candidates can be identified using the structural variant models by identifying pharmacophores or conserved features in the protein structural variant models and using this structural information to identify small molecules that would bind to the structural variant models.

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Using structural comparison tools described herein, the common structural features that are conserved across a range of structural variant models of a given protein based on different genetic polymorphisms can be identified. To do this, multiple structural variant models are compared, generally by superimposing the coordinates of one variant model onto those of one or more other variants and observing the structural fit. Such functionality is commonly found in molecular graphics or homology modeling packages. Once the optimum fit of structures is performed, then the structural features that are present throughout the structural variant models can be identified and used as the basis for drug interactions in structure-based drug design studies. For example, the pharmacophores or conserved features can be specified as database queries and a library or database of small molecule structures can be

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searched to identify new lead compounds to bind to the pharmacophores. Alternatively, other structure-based ligand design strategies can be employed to design lead compounds or to identify modifications to be made to existing drugs to improve biological activity.

4. Identification of compensatory structural changes

Certain proteins, for example, viral proteins or other infectious organisms, may harbor multiple genetic polymorphisms. Since each genetic polymorphism can give rise to slight changes in structure, some, and over time, many, additional genetic polymorphisms may cause changes in the protein structures that significantly affect biological activity. These structural changes could result in, for example, different dynamical behavior, alteration in enzyme kinetics or differences in substrate recognition, which can significantly alter drug response. For example, a mutation for one drug compound can suppress a mutation to a second drug due to compensatory effects. In these cases, a drug which is predicted to be ineffective for a given patient based upon the single nucleotide correlation may, in fact, be effective as a result of these changes.

Because mutations are so frequent in AIDS and other viruses, few sequences are exactly the same in different patients. Thus, it is difficult or inconclusive to generate multiple mutation sequence correlations for drug resistance. If each patient has a different viral sequence due to a high viral mutation rate, then no sequence correlation is even possible in such cases.

The methods described herein can be used to study the effects of multiple genetic polymorphisms on a resultant protein structure. Multiple mutations are common in AIDS and other viruses, which makes sequence correlation difficult. By observing the structural effects of the mutations on the resulting protein, it is possible to look at the net effect of all

structural changes and to consider the overall structure of the protein in drug design studies. For example, a mutation might occur in the active site, or site of drug action, in a protein. Additionally, there may be related mutations in other parts of the protein structure, which might not be identified from a single point mutation correlation. These related mutations could have an effect on biological activity of the protein. By looking only at the active site, it might be predicted that a drug or potential drug would not bind to the protein. The additional mutation, however, might cause compensatory structural changes in the protein structure that alter its properties in a way that restores biological activity.

By computing 3-D protein structures from gene sequences containing multiple polymorphisms, it is possible to more accurately predict the effect of multiple sequence mutations on protein structure and, thus, to obtain a better correlation between sequence and drug resistance than by considering sequence correlations alone. This information can be useful, for example, in understanding drug resistance and can aid researchers and clinicians in developing new drug therapies to overcome drug resistance.

The structures that are derived based on multiple generic polymorphisms can be used in structure-based drug design studies to provide frameworks, or scaffolds, into which drug or potential drug molecules can be docked. This permits the design of drugs that are active against a wider range of structural variants, thus, in more patients or against a range of drug resistant proteins.

5. Clinical Applications

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A knowledge of the repertoire of structural differences arising from genetic polymorphisms across the human population or specific subpopulations can provide insight into the differing biological responses in patients based on their genetic differences. For example, where clinical

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data are available for patients having particular genetic polymorphisms, this information can be associated with the 3-D protein structural variants and used to find correlations between polymorphisms and observed drug responses.

The methods provided herein can be used to design drug therapies that bring about favorable clinical responses (or eliminate unfavorable effects) in patients, to identify pharmacological effects of drugs in different patient subpopulations (e.g. age, race, gender) and to simulate clinical trails to increase the probability that the trials will yield optimal results.

Because of the high cost of clinical trials, such studies are generally focused on small patient populations. The structural analysis tools described herein permit the extension of clinical trials to cover patient populations not specifically included in the study. This is accomplished through correlation of the structural variants derived from genetic polymorphisms with clinical responses.

The molecular structures and databases described herein can also find application in the understanding and prediction of clinical or pharmacological drug responses, for example, efficacy, toxicity, dose dependencies or side effects in patients. For example, relational databases containing 3-D protein structural variants can provide a means for managing and using the information to understand and predict clinical responses in patients.

In other embodiments, observed clinical data from patients in a clinical trial can be associated with the structural variant models for each genetic polymorphism exhibited in the clinical subjects, for example, in a structural polymorphism relational database. The correlation between the structural variants and observed clinical effects can then be utilized to predict clinical outcomes in patients that did not participate in the clinical

trial. For example, a structural variant model can be generated for a patient based on a genetic polymorphism exhibited in the patient, and the database can be mined to identify structurally similar variants for which clinical results are known. Structural similarity can be determined, for example, by superimposing the structures and measuring the RMS (root mean squared) differences between the structures or by using pattern matching or motif searching algorithms. The results can be used to predict clinical responses in the patient based on the clinical data associated with the structurally similar variants.

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The predicted correlations can also be used to aid in the design of subsequent clinical trials. The follow-on trials can be made more effective through the judicious selection of patients with given genotypes (i.e., those exhibiting the same genetic polymorphisms), as guided by the structurally predicted outcomes. For example, a clinical trial can be designed based on a subpopulation of clinical subjects which exhibit a specific genetic polymorphism (i.e. structural variant) to demonstrate the effectiveness of a given therapeutic on a targeted population.

In other embodiments, the methods provided herein can be used in the selection of drug therapies for patients exhibiting a particular genetic polymorphism. This is accomplished by generating the structural variant model associated with the polymorphism, docking drug molecules that might be used to treat the patient into the structural variant model and calculating the binding energies of each drug with the variant. The results of docking or free energy calculations can be correlated to clinical data, for example, patient population (e.g., ethnic background, race, sex, age), treatment regimen, patient response to a particular drug or duration of treatment. The binding energies can be compared, for example, to determine which drug would best bind to the variant in order to identify

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the drug that could best be used to treat the patient to optimize biological activity.

D. Creation of 3-D Structural Polymorphism Databases

The above-noted methods all rely upon the use of databases of nucleic acid sequences. Any such database known to those of skill in the art may be employed; numerous such databases are publically available (e.g. the Stanford HIV database). The Stanford HIV database is hierarchal database with information about HIV patients who received or did not receive protease inhibitor treatments, patient-dates, isolates, sequences, hyperlinks to MEDLINE and GenBank abstracts, and art. This database, however, does not contain 3-D protein structures of any proteins including HIV reverse transcriptase (RT) and HIV protease (PR; see, e.g., Shafer et al. (1999) Nucleic Acids Res. 27:348-352, Shafer et al. (1999) J. Virol 73:6197-6202, http://hivdb.stanford.edu/hiv, Richter (January 20, 1999) "AIDS drugs found to be effective in the world's most common HIV strains).

Databases of sequences and associated information may also be generated as described herein by obtaining samples and sequences from a variety of sources. In all instances, further databases are generated by then calulating 3-D structural models of the encoded proteins or relevant portions, such as active binding sites, thereof, from the nucleic acid sequence information. It is these databases of nucleic acid sequence and/or primary protein sequence and the associated 3-D structure that are provided herein and that are used in the all of the methods, except for the computational phenotyping discussed below, which does not require a database, provided herein. Hence databases comtaining computationally determined 3-D structures of polymorphic proteins or portions thereof are provided herein. These databases serve as tools in a variety of methods, including those provided herein.

-54-

Databases that include 3-D structures for variant proteins encoded by the nucleic acids that contain polymorphisms are provided. These are generated after 3-D structural models are constructed for the protein structural variants, preferably for all of the protein structural variants, representing the genetic polymorphisms, by inputting the atomic coordinates into a structural polymorphism database, preferably a relational database, and optionally with associated structural and/or physical properties (e.g., phi/psi and side-chain angles and energetics), and other data, if available, including, but are not limited to, historical data, such as parental medical histories, and clinical data. The resulting database is used in structure-based drug design studies and for clinical analyses. Figure 11 is a tabulation of the 3-D coordinates of a representative entry, an HIV protease, that is encoded by the DNA in one of SEQ ID Nos. 3-74 and 77-117, and that is an entry in an exemplary database that includes 3-D structures. Exemplary databases that contain the nucleic acids sequences and structures of all proteins encoded by SEQ ID Nos. 3-117 as well additional nucleic acids are provided herein and are described in the EXAMPLES.

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A database is preferably interfaced to a molecular graphics package
that includes 3-D visualization and structural analysis tools, to analyze
similarities and variations in the protein structural variant models (see,
copending U.S. application Serial No. 09/531,995, which is published as
International PCT application No. WO 00/57309, and is a continuation-inpart of U.S. application Serial No. 09/272,814, filed March 19, 1999).
Briefly, International PCT application No. WO 00/57309 provides a
database and interface for access to 3-D molecular structures and
associated properties, which can be used to facilitate the design of
potential new therapeutics. The interface also provides access to other

structure-based drug discovery tools and to other databases, such as

databases of chemical structures, including fine chemical or combinatorial libraries, for use in structure-focused high-throughput screening, as well as to a host of public domain databases and bioinformatics sites. The interface also provides access to other structure-based drug discovery tools and to other databases, such as databases of chemical structures, including fine chemical or combinatorial libraries, for use in structure-focused high-throughput screening, as well as to a host of public domain databases and bioinformatics sites. This interface can be modified as needed to adapt for use with a particular database.

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A relational database that collects multiple data files relating to the same molecular structure in the same subdirectory and that provides an interface to access all of the collected files from the same structure using the same user interface program is also provided. The collected files include a variety of information and computer file formats, depending on the type of information to be conveyed to users of the database. In practice, a user communicates over a public network, such as the Internet, or over a controlled network, such as an internet, with a secure file server that controls access to the collected files, and the interface to the collected files is provided by a standard graphical user interface program that is widely available. In this way, a convenient means of searching molecular structure data for characteristics of interest is provided. Data searching, file viewing, and investigation of multiple representations of molecular structures from within a single viewing program can also be performed using the database and interface.

The data files can be those available over a wide network such as the Internet, and a suitable graphical user interface designed or obtained. Such interface is used for viewing the data files is a standard Internet web browser program, such as the web browser products by Netscape Communications, Inc. and Microsoft Corporation that are distributed free

of charge. Such browser products readily import and provide views of files having a wide variety of formats that contain alphanumeric, video, and audio data. A security server is preferably located between the user browser program at a network client machine controls access to the database, which is housed at a file server connected to the security server. Before a user gains access to the database, the security server checks authorization for the individual user and then, if appropriate, permits downloading of appropriate data from the database file server. It is contemplated that the databases containing 3-D structures of proteins or portions thereof the exhibit polymorphism will be loaded.

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Data for a molecular structure is loaded into the database by specifying the file pathnames for the various data files that contain the different types of data, including the different molecule views. Using a browser to view the data files permits various helper applications, called plug-ins, to smoothly and transparently accept the different file formats and provide views to the user. The various data files of the database are organized in accordance with the database design when they are loaded into the database and are managed by a relational database management program.

In addition to 3-D protein structures and associate primary sequences, as provided herein, the database can optionally contain associated biological or clinical data, such as drug resistance, side effects, efficacy, pharmacokinetics and other data, that correlate with or can be correlated the structural variants. This information will be used for correlating observed clinical effects to specific structural variants and for predicting clinical responses and outcomes based on a patient's structural variants, *i.e.*, genetic polymorphisms.

-57-

Structural analysis tools are preferably integrated with the structural database for comparing and analyzing the resulting protein structural variant models. For example, the molecular graphics software package described in International PCT application No. WO 00/57309, includes structural analysis capability to measure the structural attributes of the model (distances, angles, etc.), to analyze sequences and secondary structures, to study physical properties such as hydrophobicity, electrostatic potential, and active or reactive sites in the protein, as well as to evaluate the quality of the structure (both conformationally and energetically).

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Structures can also be compared by aligning them, such as by performing a least squares fitting of the x-, y- and z-coordinates of each of the structural variant models and superimposing the structures or any other alignment method or structural comparison method. For example, the structures of the variants can be clustered, or grouped together, based on structural similarity. This can save time over studying each structural variant independently because, where structures are considered to be similar enough that they are clustered together (e.g., if their structures can be superimposed within a specified tolerance), then only a representative structure, or perhaps an average structure or scaffold, which is derived as a composite of the individual structural variant models, can be used in further drug design studies.

Tools for database searching can also be included in the software package. These can be used to query the database for structural variant models having similar properties, such as molecular structure or sequence similarity. These tools are used, for example, to mine the database to identify variant models that are structurally similar (e.g. to find structures that overlap within a specified tolerance), and thus would be predicted to interact in the same way with potential drugs or exhibit the same clinical

response. This information could be useful in understanding the structural or clinical effects of different genetic polymorphisms and could potentially save time and money by extending the results of previously performed clinical or computer-based drug design studies to predict the results of studies on similar structural variants that have not yet been performed.

1. Exemplary Databases

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Databases containing data representative of the 3-D structure of structural variants encoded by a selected gene or genes or the 3-D structure of other polymorphic variants are provided. The selected genes can be drug target, such as receptors and genes of infectious agents, such as the HIV protease or reverse transcriptase. Exemplary databases are presented in Example 5 which describes the construction, interface, use and appliations of HIV PR and RT databases. These databases may be stored on any suitable medium and used in any suitable computer system. Systems and methods for generating, storing and processing databases are well known.

2. Computer systems

Computer systems for processing the databases and computer systems containing the databases are provided. The processing that maintains the database and performs the methods and procedures using the databases may be performed on multiple computers, or may be performed by a single, integrated computer. For example, the computer through which data is added to the database may be separate from the computer through which the database is sorted or analyzed, or may be integrated with it. Each computer operates under control of a central processor unit (CPU), such as a "Pentium" microprocessor and associated integrated circuit chips, available from Intel Corporation of Santa Clara, California, USA. A computer user can input commands and data from a

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keyboard and display mouse and can view inputs and computer output at a display. The display is typically a video monitor or flat panel display device. The computer also includes a direct access storage device (DASD), such as a fixed hard disk drive. The memory typically includes volatile semiconductor random access memory (RAM). Each computer preferably includes a program product reader that accepts a program product storage device from which the program product reader can read data (and to which it can optionally write data). The program product reader can include, for example, a disk drive, and the program product storage device can comprise removable storage media such as a magnetic floppy disk, an optical CD-ROM disc, a CD-R disc, a CD-RW disc, or a DVD data disc. If desired, computers can be connected so they can communicate with each other, and with other connected computers, over a network. Each computer can communicate with the other connected computers over the network through a network interface (see, e.g., Examples below) that permits communication over a connection between the network and the computer.

The computer operates under control of programming steps that are temporarily stored in the memory in accordance with conventional computer construction. When the programming steps are executed by the CPU, the pertinent system components perform their respective functions. Thus, the programming steps implement the functionality of the system as described above. The programming steps can be received from the DASD, through the program product reader, or through the network connection. The storage drive can receive a program product, read programming steps recorded thereon, and transfer the programming steps into the memory for execution by the CPU. As noted above, the program product storage device can include any one of multiple removable media having recorded computer-readable instructions,

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including magnetic floppy disks and CD-ROM storage discs. Other suitable program product storage devices can include magnetic tape and semiconductor memory chips. In this way, the processing steps necessary for operation can be embodied on a program product.

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Alternatively, the program steps can be received into the operating memory over the network. In the network method, the computer receives data including program steps into the memory through the network interface after network communication has been established over the network connection by well known methods that will be understood by those skilled in the art without further explanation.

The computer that implements the client side processing, and the computer that implements the server side processing, or any other computer device of the system, may comprise any conventional computer suitable for implementing the functionality described herein. FIGURE 9 is a block diagram of an exemplary computer device 900 such as might comprise any of the computing devices in the system. Each computer operates under control of a central processor unit (CPU) 902, such as an application specific integrated circuit (ASIC) from a number of vendors, or a "Pentium"-class microprocessor and associated integrated circuit chips, available from Intel Corporation of Santa Clara, California, USA. Commands and data can be input from a user control panel, remote control device, or a keyboard and mouse combination 904 and inputs and output can be viewed at a display 906. The display is typically a video monitor or flat panel display device.

The computer device 900 may comprise a personal computer or, in the case of a client machine, the computer device may comprise a Web appliance or other suitable Web-enabled device for viewing Web pages. In the case of a personal computer, the device 900 preferably includes a direct access storage device (DASD) 908, such as a fixed hard disk drive (HDD).

-61-

The memory 910 typically comprises volatile semiconductor random access memory (RAM). If the computer device 900 is a personal computer, it preferably includes a program product reader 912 that accepts a program product storage device 914, from which the program product reader can read data (and to which it can optionally write data). The program product reader can comprise, for example, a disk drive, and the program product storage device can comprise removable storage media such as a floppy disk, an optical CD-ROM disc, a CD-R disc, a CD-RW disc, a DVD disk, or the like. Semiconductor memory devices for data storage and corresponding readers may also be used. The computer device 900 can communicate with the other connected computers over a network 916 (such as the Internet) through a network interface 918 that enables communication over a connection 920 between the network and the computer device.

The CPU 902 operates under control of programming steps that are temporarily stored in the memory 910 of the computer 900. When the programming steps are executed, the pertinent system component performs its functions. Thus, the programming steps implement the functionality of the system illustrated in FIGURE 1. The programming steps can be received from the DASD 908, through the program product 914, or through the network connection 920, or can be incorporated into an ASIC as part of the production process for the computer device. If the computer device includes a storage drive 912, then it can receive a program product, read programming steps recorded thereon, and transfer the programming steps into the memory 910 for execution by the CPU 902. As noted above, the program product storage device can comprise any one of multiple removable media having recorded computer-readable instructions, including magnetic floppy disks, CD-ROM, and DVD storage discs. Other suitable program product storage devices can include magnetic tape and semiconductor

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memory chips. In this way, the processing steps necessary for operation in accord with the methods herein can be embodied on a program product.

Alternatively, the program steps can be received into the operating memory 910 over the network 916. In the network method, the computer receives data including program steps into the memory 910 through the network interface 918 after network communication has been established over the network connection 920 by well-known methods that will be understood by those skilled in the art without further explanation. The program steps are then executed by the CPU 902 to implement the processing of the system.

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To implement the functionality described herein, it has been found that a suitable computer for performing database server tasks includes a "Pentium" level CPU having at least 128 MB of memory, 30 GB of disk storage, and 256 MB of disk swap space for files. A recommended 15 configuration for computer performance would include, for example, a "Pentium III" processor at 700 MHz or faster, memory of 256 MB or greater, disk storage space of 50 GB or more, and swap space of 500 MB or more. A suitable configuration for performing user tasks as described above includes a "Pentium" level CPU having 128 MB memory, disk space of 240 MB with swap space of 256 MB, and an optional display circuit card supporting OpenGL and having 4 MB of memory. A recommended configuration includes, for example, a "Pentium III" processor at 500 MHz or faster, memory of 256 MB or greater, disk space of 500 MB or more, swap space of 500 MB or more, and an optional display card having 8 MB of memory or more, supporting resolution of 1024 x 768.

In a preferred embodiment, the software used in the computing system described above includes, for the server machine, operating system software such as "Windows NT Server 4.0" from Microsoft

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Corporation, with Service Pack 5, Version 1280 (10 June 1999) or more recent, with database management server software such as, but are not limited to, "Oracle Server Standard Edition 8.1" from Oracle Corporation. The software used in a preferred embodiment of the user machine includes operating system software such as "Windows NT Workstation 4.0" from Microsoft Corporation, with Service Pack 5, version 1280 (10 June 1999) or more recent, as well as "Oracle Client Standard Edition Version 8.1" or higher. The client machine will also be compliant with the "Java" programming language (Java Runtime Environment 1.2.2). As will be known to those skilled in the art, other configurations may be suitable, depending on the applications being used and the computer performance desired.

E. Computational phenotyping

Also provided herein is a method designated computational 15 phenotyping. Computational (also referred to herein as in silico phenotyping). This refers to the method in which a 3-D protein structure is generated from a given genotype and protein-drug binding analyses in silico (computationally) are performed in order to determine whether drug binding does (i.e. sensitive) or does not (i.e. resistant) take place. This type of analysis is contemplated to be performed for an individual patient 20 or subject or groups thereof, such as ethnic groups, gender-based or agebased groups, particular species or groups thereof) to assess or select a drug for treatment of a particular disease or other such use, and is done to assess efficacy of a particular drug on a desired target, where the target exhibits polymorphisms. The following discussion and example, below, is with reference to HIV PR and RT, but it is understood that the methods and applications can be applied to any protein or gene product that exhibits polymorphic variation, and particularly to gene products that are drug targets.

Among the methods of computational phenotyping, there are three distinct methodologies that are clinically useful for determining either resistance or sensitivity to particular HIV-1 antiviral therapeutics. These are: genotyping, phenotyping, and *virtual* phenotyping. These methodologies are used to optimize the choice of therapeutics during the initiation of therapy, after drug failure, and/or during salvage therapy. Genotyping involves extracting the HIV viral RNA and amplifying all or part of the genes encoding the protease and reverse transcriptase proteins and sequencing them in order to assess the presence of resistance-associated mutations.

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In phenotyping, the amplified sequences are instead sub-cloned into expression vectors and then tested for their replicative ability in vitro by transfecting them into cultured and/or established cell lines, such as, for example, human T cells, monocytes, macrophage, dendritic cells, Langerhans cells, hematopoeitic stem cells, HeLa, XC, Mm5MT, LTL, COS 7, NIH3T3, LTA, MCF-7, or other cells derived from human tissues and cells that which are the principal targets of viral infection in the presence or absence of antiviral drugs (see, e.g., U.S. Patent No. 5,837,464; see, also EP 0852626; EP 1012334; and EP 0877937), 20 Virtual phenotyping (ViroLogic, Inc.) is an interpretive service in which the phenotype of a specimen (i.e. of a plant, animal, pathogen, or human) is inferred from the specimen's genotype based upon an extensive correlative database of known genotypes and phenotypes. Such a correlative database must be updated constantly to maintain clinical 25 accuracy.

Similar to *virtual* phenotyping, computational or in *silico* phenotyping infers phenotype based upon specimen genotype. Computational phenotyping is distinct from *virtual* phenotyping in that sensitivity or resistance to drugs is determined directly through protein-drug binding

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analysis performed in silico and not through correlation with a database of known genotypes and phenotypes. The advantage of computational phenotyping is that new resistance conferring mutations can be discovered rapidly and in "real time" without the need for phenotyping to train the genotype. Moreover, in silico phenotypes are not subject to error caused from compensatory mutations which may act synergistically or anti-synergistically with resistance-associated mutations to increase, decrease, or reverse specific drug resistances. Computational phenotyping will generate information that can, for example, be presented in a report that is marketed within the in vitro diagnostics industry as an adjunct test/service to help optimize therapy and assist physicians, farmers, acadmenic institutions, government agencies, and industries with specimen treatment. Thus, a computer-based method for predicting clinical responses e.g. drug sensitivity or drug resistance in patients, plants, animals, pathogens, and microorganisms based on genetic polymorphisms is provided.

The genotypes used in the methods are obtained from any source, including, but are not limited to, from a plant, animal, pathogen, or mammal with the most preferred source being a mammal, paticularly a human for whom a particular drug treatment is contemplated, and is the genotype of the drug target, such as, as exemplified herein, HIV RT or PR from a particular infected individual. Other examplary drug targets are proteins, polypeptides, oligopeptides, including, but not limited to, a receptor, enzyme, hormone, and any such compound with which drugs or other ligands interact to bring about a biological response. For exemplification of this method, the protein considered is an enzyme, in particular HIV protease (PR) and reverse transcriptase (RT), which are therapeutic drug targets. Nucleic acid encoding the target from individual sample, such as blood sample or other body fluid sample from a

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mammal, such as a human patient, is sequenced, and the 3-D structure thereof determined. The drug of interest is computationally tested to assess whether it interacts with the sample.

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

EXAMPLE 1

BINDING CORRELATIONS OF MUTANT FORMS OF HCV PROTEASE WITH DIFFERENT INHIBITORS

This example provides the results of a theoretical study of NS3 protease complexes with two known peptide inhibitors (see SEQ ID Nos. 1 and 2; Ingallinella *et al.* ((1998) *Biochemistry 37*:8906-8914).

Introduction

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During HCV replication, the final steps of processing are performed. by a virially encoded chymotrypsin-like serine protease NS3. NS3 is an approximately 3000 amino acid protein that contains, from the amino terminus to the carboxy terminus, a nucleocapsid protein (C), envelope proteins (E1 and E2) and several non-structural proteins (NS1, 2, 3, 4a, 4b, 5a and 5b). NS3 is an approximately 68 kDa protein, encoded by approximately 1893 nucleotides of the HCV genome, and has two distinct domains: (a) a serine protease domain containing approximately 200 of the N-terminal amino acids; and (b) an RNA-dependent ATPase domain at the C-terminus of the protein. The NS3 protease is considered a member of the chymotrypsin family and is a serine protease that is responsible for proteolysis of the polypeptide (polyprotein) at the NS3/NS4a, NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions responsible for generating four viral proteins during viral replication. This protease is inhibited by N-terminal cleavage products of substrate peptides. The NS3 protease, which is necessary for polypeptide processing and viral replication has been identified, cloned and expressed (see, e.g., U.S. Patent No. 5,712,145).

Active NS3 forms a heterodimer with a polypeptide cofactor NS4A. The crystal structure of NS3 with and without the NS4A cofactor is known (see, e.g., Love et al. (1996) Cell 87:331-342; Habuka et al. (1997) Jikken Igaku 15:2308-2313; Yan et al. (1998) Protein Sci. 7:837-847, which provides the structure with NS4A).

The NS3 protease is a target for design of antiviral drugs. For example, a series of potent hexapeptide inhibitors of NS3 has been developed by optimization of the product inhibitors (Ingallinella *et al.* (1998) *Biochemistry 37*:8906-8914).

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Analyses

Models of the complexes of NS3 with the two protease inhibitor peptides were obtained by flexible docking of the peptides into the active site of the crystal structure of NS3/4A, followed by evaluation of protein-peptide binding energies. The models were tested by *in situ* modification of the docked ligands. A qualitative agreement between the binding energies and inhibitor IC_{50} values obtained from literature was found.

The peptides studied were:

	Sequence	IC⁵º, nM	SEQ ID
20	Ac-Asp¹-D-Glu²-Leu³-lle⁴-Cha⁵-Cys ⁶ -COO-	15	1
	Ac-Asp¹-L-Glu²-Leu³-lle⁴-Cha⁵-Cys⁴-COO-	60	2

• Cha = β -cyclohexylalanine

In the modeling studies, it was assumed that:

the high-affinity inhibitory peptides 1 and 2 have a similar mode of binding to the active site of NS3;

the minimum binding pharmacophore includes the SH group of Cys⁶ and carboxyl groups of Asp¹, Glu² and Cys⁶; and

the side chains of residues 3, 4 and 5 may enhance binding by non-specific hydrophobic interaction with NS3.

Methods

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Initial structure of the NS3-peptide complex

The crystal structure of NS3 with a peptide cofactor NS4A was obtained from the arts (Kim et al. (1996) Cell 87:343) and was used in the studies with peptide inhibitors. The crystal structure of NS3/NS4A was regularized using molecular mechanics described herein. Initial NS3-NS4-peptide complexes were constructed by placing the peptides into the NS3 binding site expected by structural homology to by other serine proteases:

the C-terminal carboxyl was placed near the oxyanion-stabilizing site (residues 137-139);

the side chain of Cys⁶ was inserted into the hydrophobic cavity formed by L135, F154 and A157; and

the ϵ -amino group of K136 was placed in contact with the C-terminal carboxyl (see, Kim et al. (1996) Cell 87:343, Steinkuhler *et al.* (1998) *Biochemistry* 37:8899).

Monte Carlo simulations

In order to optimize the complexes, Biased Based Probability Monte Carlo (BPMC) simulations (Abagyan et al. (1994) J. Mol. Biol. 235:983)

20 were performed on the NS3-peptide complexes using the ICM program (commercially available from MolSoft, San Diego, CA) with ECEPP/3 force field and atomic solvation energies (Momany et al. (1975) J. Phys. Chem. 79:2361, Nemethy et al. (1992) J. Phys. Chem. 96:6472, Abagyan et al. (1997) Computer Simulations of Biomedical Systems: Theoretical and Experimental Applications, vol. 3, Kluwer Academic Publishers, Dordrecht, The Netherlands, p. 363). The sampling method was BPMC with random change of one variable at a time. A Metropolis acceptance criterion was applied after energy minimization (quasi-Newton, up to 1000 steps). Simulations were performed at a temperature of 1000° K. The

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peptide translational and rotational degrees of freedom, all peptide torsion angles and χ angles of the protein side-chains located within 7.0 Å of any peptide atom were varied during the BPMC simulations.

The energy function used in the MC simulations included:

ECEPP/3 terms for energy in vacuo (VDW (van der Waals), H-bond, electrostatic and torsion potentials);

distance dependent electrostatics with $e_0 = 4.0$; and surface energy with atomic solvation parameters.

The total energies of the complexes were calculated including contributions from: ECEPP/3 VDW, H-bond, S-S bond and torsion terms; exact-boundary electrostatic energy with $e_0=8.0$; and side-chain entropies. Hydrophobic free energies were estimated as sA, where A is accessible surface area and s is a tension constant of 0.03 kcal/molÅ².

Strategy of the flexible Monte Carlo docking

The simulations proceeded with multiple, relatively short MC runs (2000-5000 generated structures). New docking cycles were started from the lowest-energy or other interesting structures found in previous runs. Structures saved during various MC runs were sorted by total energies and RMSD (root-mean-squared deviation), and compressed into a cumulative conformational stack. Binding energies were calculated for representative structures of each complex thus obtained. This strategy was more efficient than continuous long simulations because the variable torsion angles and distance constraints are defined for an initial structure and do not change during the MC run.

Binding energies of the peptide-protein complexes

For low-energy conformations found after several iterative BMPC cycles, peptide-protein binding energies were estimated using the equation:

$$E_{bind} = E_{o} + E_{compl} - E_{pept} - E_{prot}$$

where E_{compl} is the energy of the complex, E_{pept} & E_{prot} are separate energies of the peptide and protein, respectively, and E_{o} is an adjustable constant.

The binding energy function included: exact-boundary electrostatic free energy contributions; side-chain entropy; and surface tension hydrophobic free energy terms. (Zhou and Abagyan (1998) Folding Design 3:513, Schapira *et al.* (1999) J. Mol. Recognition 12:177). ECEPP/3 hydrogen-bonding terms were included with a weight of 0.5.

Results

Models of the NS3-peptide complexes

RMSD between pharmacophore atoms of peptides 1 and 2 were calculated for all pairs of BPMC structures. Two models of the NS3-peptide complexes were selected assuming (1) similar positions of pharmacophore groups of two peptides in the binding site (RMSD \leq 2.0 Å) and (2) low binding energy of the complexes ($\Delta E_{bind} < 5.0$ kcal/mol). Two models of the NS3-peptide complex were selected by visual inspection.

Characteristics of the binding sites for peptide inhibitors in two NS3-peptide complex models are summarized in **Table 1**.

Table 1

Peptide site NS3 residue, group Type of Present for Peptide Model 1 residue Model 2 interaction P1 Cvs⁶COO⁻ $K136 NH_3 +$ H-bond/el. 1,2 1,2 **G137 NH** H-bond 1,2 2 S139 OH H-bond 1,2 2 Cys⁶ SH L135, F154, A157 1,2 1,2 hydroph P2 Cha⁵ H57, R155, A156 hydroph 1,2 A157, V158 2 hydroph **P3** lle⁴ V132, S133 1,2 2 hydroph V158, C159 hydroph 1

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P4	Leu ³	Res. 157 to 160 V132, S133	hydroph hydroph	1,2	2 . 1
P5	Glu ² COO-	R161 guanidine	H-bond/el.	-	1,2
P6	Asp ¹ COO-	R161 guanidine S133 OH	H-bond/el. H-bond	1,2	- 1,2

Validation of the models: modifications of the protein and ligands in the binding site

In order to validate the proposed models, the K136M mutation and peptide modifications known from SAR (structure-activity relationship) studies were performed in low-energy structures of the NS3-peptide 2 complex.

Positions of the modified ligand and conformations of adjacent protein side chains were adjusted by energy minimization. Distance restraints were applied to keep the ligand near its initial position.

Changes in calculated binding energies upon modifications, ΔE_{bind} (calc), were compared to the values expected from ratios of inhibitory potencies, ΔE_{bind} (exp).

$$\Delta E_{bind}(exp) = RT \ln(IC_{50}^{mod}/IC_{50}^{o}),$$

where IC_{50}° and IC_{50}^{mod} are inhibitory potencies of the parent and modified compounds.

The correlation between experimental and calculated changes in binding energy upon ligand modifications in the binding site of NS3 is illustrated in

FIG. 4.

Discussion

25 The two NS3-peptide complex models suggest a common binding pattern for the inhibitor P1 site (Cys⁶-OH) with the carboxyl group hydrogen-bonded to the oxyanion hole residues G137 and S139, and the

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Cys⁶ side chain embedded in a hydrophobic pocket formed by L135, F154 and A157.

This study confirms the possibility of hydrogen bonding between the C-terminal carboxyl and ϵ -amino group of K136 suggested by Steinkuhler *et al.* ((1998) *Biochemistry* 37:8899) based on the K136M mutation in NS3. Changes in calculated binding energies upon mutation are consistent with an 8-fold increase in K_1 of an inhibitor with a free carboxyl group and with the lack of an effect on binding when the peptide is amidated.

The models differ in binding of the negatively charged side chains in positions P5 and P6. The R161 guanidine interacts with a carboxyl group of Asp¹ and Glu² in Models 1 and 2, respectively. In Model 2, the Asp¹ carboxyl also interacts with the hydroxyl of S133.

The models are in agreement with SAR data for peptide inhibitors of NS3. Predicted changes in binding energy upon modification of the protein and peptides correlate reasonably well with the changes expected from IC⁵⁰ ratios. Standard deviations of $\Delta E_{bind}(calc)$ - $\Delta E_{bind}(exp)$ were 0.8 and 1.6 kcal/mol for Models 1 and 2, respectively, with correlation coefficients of 0.62. After the largest outlier was removed from each dataset, correlations improved to 0.81 and 0.76, respectively.

Conclusions

An effective iterative Biased Probability Monte Carlo protocol for the docking of flexible peptide ligands into a flexible protein active site has been developed. Two models of the complexes of HCV NS3 protease with potent peptide inhibitors were proposed based on the docking simulations and on evaluation of protein-ligand binding energies. The models were validated by *in situ* modifications of NS3-peptide complexes and by correlation of binding energies of modified complexes with those expected from experimental IC₅₀ values. Proposed models can be used

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for planning further mutagenesis studies of the HCV NS3 protease and the models can be used in the design of non-peptide inhibitors using structure-based drug design methodologies.

EXAMPLE 2

LEAD OPTIMIZATION BY RECEPTOR-BASED FREE ENERGY QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIPS (QSARS) FOR TNF RECEPTOR ANTAGONIST DISCOVERY

The goal of the modeling studies in this phase was to identify binding modes and complex structures of the compounds that bind to TNF receptor type I protein in order to guide the design of new compounds. An approach that relies on docking compounds to the receptor, evaluating free energy changes of binding of the docked structures, and comparing the calculated values with experimental inhibition constants K_i of the compounds was developed. The success of the calculations was assessed by evaluating the consistency of the calculated free energy changes of binding and the experimental K_i .

The difference in free energy changes of binding between two compounds with inhibition constants K_i and K_i^{\prime} can be calculated as,

 $\Delta\Delta G = -kT \ln K_i'/K_i$

where k and T are Boltzmann's constant and absolute temperature, respectively.

The 13 active compounds were studied. Their potencies, as measured by K_i , range from 0.1 to 30 μ M, spanning about 3 kcal/mol in free energy. It was found that the calculated free energy changes of binding are highly consistent with the corresponding experimental values, with correlation coefficient 0.966 and difference less than 0.5 kcal/mol (see Table 2 and Figure 4). The predicted binding modes and complex structures can thus be accepted with confidence.

To modify these compounds, important pharmacophore features on the surface of the receptor that are critical for binding of the compounds

were identified. These features include a hydrophobic belt, a hydrophilic belt and 3 hydrogen bond donor sites. A few of potential hydrogen bonding sites, which are not used by the current compounds, were also derived, and can be used for designing more potent binders.

Graphics-guided redesign of the compounds was performed. The free energy calculation was used to predict the binding activity of each design. Fourteen new compounds were thus designed and binding activities were predicted. The chemical structures of the designed molecules, together with the binding modes of the lead compounds, were synthesized and shown to have high affinity for the target. Some of them exhibit a K_i in low-nanomolar range. Hence the method provided herein for modification of drugs for binding to calculated 3-D structures of a target protein resulted in redesigned drug candidates with enhanced affinity for the target.

This approach has advantages over the traditional x-ray crystallography method, which include the following:

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- (1) The binding modes are determined for a group of compounds instead of single compound; analysis of similarity and differences reveals rich information in binding mechanisms.
- (2) The predictive power of the free energy calculation is very desirable for redesign of compounds.
- (3) The correlation with the biochemical activities assures relevancy of the explored binding modes, while a structure given by x-ray crystallography may not necessarily be one related to the biological functions of the compound.

A comparison of calculated relative free energy changes of binding $\Delta\Delta A$ and experimental $\Delta\Delta G$ converted from inhibition constants K_i (all in kcal/mol) of the compounds (referenced by a code name) is presented in Table 2.

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Table 2

Compound	ΔΔΑ	ΔΔG
SBI-2030	0	0
SBI-2002	-0.97	-1.25
SBI-2005	-0.72	-1.14
SBI-307	-0.56	-0.08
SBI-2008	-0.53	-0.82
SBI-2006	-0.34	-0.44
SBI-306	-0.07	0.40
SBI-2000	0.29	0.27
SBI-2001	0.72	1.12
SBI-304	1.55	1.45
SBI-308	1.70	1.78
SBI-305	1.86	1.67
SBI-2048	1.95	1.94

A comparison of calculated *versus* experimental binding free energy changes is given in FIG. 5.

EXAMPLE 3

20 HIV Protease Models for Drug Studies

Antiviral therapy for AIDS has focused on the discovery and design of inhibitors for two main enzyme targets of the HIV-1: reverse transcriptase (RT) and protease (PR). HIV RT is a heterodimer composed of p51 and p66 subunits. The p51 subunit is composed of the first 450 amino acids encoded by the RT gene and the p66 subunit is composed of all 560 amino acids of the RT gene. RT is responsible for RNA-dependent DNA polymerization, RNaseH activity, and DNA-dependent DNA polymerization.

-76-

HIV PR is a homodimer of two identical 99-amino acid chains. HIV PR is an aspartic proteinase that is responsible for the post-translational processing of the viral gag and gag-pol polyprotein gene products, which yields the structural proteins and enzymes of the viral particle (see, e.g., Erickson et al. (1996) Annu. Rev. Pharmacol. Toxicol. 36:545-571, Bouras et al. (1999) J. Med. Chem. 42:957-962). Despite several promising new anti-HIV agents, the clinical emergence of drug-resistant variants of HIV limits the long-term effectiveness of these drugs. Genetic analysis of the resistant forms of HIV has identified a number of critical mutations in the RT and PR genes. Moreover, structural analysis of inhibitor-enzyme complexes and mutational modeling studies can lead to a better understanding of how these drug-resistant mutations exert their effects at the structural and functional levels.

HIV-PR inhibitor computational binding studies

This example provides the results of a computational study on HIV PR. The 3-D protease structure was generated, docked with known viral inhibitors, and analyzed via free energy of binding studies described herein. A quantitative agreement between the calculated add experimental protease-drug binding energies was obtained. Moreover, a series of 3-D HIV PR models were analyzed to identify the invariant regions of the protease. These insights have implications for the design of new drugs and therapeutic strategies to combat AIDS drug resistance.

Optimization of 3D structures

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Five PR inhibitors approved by the FDA for clinical use were used: saquinavir, nelfinavir, indinavir, amprenavir, and ritonavir (Figure 6). Initial 3-D structures for the wild-type HIV PR complexes with these FDA approved inhibitors were obtained from the Protein Data Bank and were then optimized using Monte Carlo (MC) simulations with an ECEPP/3 force field as described in Example 1. The energy function used in the

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MC simulations included: ECEPP/3 terms for energy in vacuo (van der Waals, H-bond, electrostatic and torsion potentials); distance dependent dielectrics with $e_0 = 4.0$; and surface free energy calculated using atomic solvation parameters ((Dudek et al. (1998) J. Computational Chem. 19:548-573, Wang et al. (1995) J. Mol. Biol. 253:473-492). Standard ECEPP charges were used for the protein residues. Lys, Arg, Glu, and Asp residues were charged. Charged and protonated states of Asp 125 (chain B) were considered as well. The inhibitors were docked into the active site of the protease, and the protein-drug complexes were energetically refined using the methods described in Example 1. Partial charges for the inhibitors were calculated with the Gasteiger-Marsili method implemented in SYBYL 6.5 (Tripos Assoc., Inc.). Different protonation states were examined for indinavir and amprenavir, but the other inhibitors were assumed to be electroneutral. Water molecules located within 7.0 Å from a ligand atom in the X-ray structure were retained in the model complex during optimization.

Calculation of binding energies

For low energy conformations found after several iterative BMPC cycles, protein-drug binding energies were estimated using the equation:

 $E_{bind} = E_o + E_{compl} - E_{ligand} - E_{prot},$ where E_{compl} is the energy of the complex, E_{ligand} & E_{prot} are energies of the ligand and protein when separated, and E_o is an adjustable constant. The binding energies of the protein and ligand were calculated using the following energy function:

 $E = E_{el} + E_{vw} + E_{hb} + E_{s},$

where $E_{\rm el}$ is the exact-boundary electrostatic using $e_0=8.0$, $E_{\rm s}$ is the side-chain entropy term, and $E_{\rm vw}$ and $E_{\rm hb}$ are the ECEPP/3 van der Waals and hydrogen-bonding terms.

After the energies of the wild type PR-inhibitor complexes were calculated, mutation sites were introduced into the optimized X-ray structures or model complexes. The amino acid substitutions were followed by local optimization, using an ECEPP/3 force field, of protein side chains around the mutation sites via the energy minimization of substructures that included the ligand, water molecules within the sphere of radius 7.0 Å around the ligand, and protease residues within the sphere of radius 3-5 Å around the mutated residues. The energy of binding of the mutated complex was calculated based on the equation described herein. The difference in binding energy resulting from mutations (mut) of the wild-type (WT) protease were calculated using the following equation:

 ΔE_{bind} (calculated) = E_{bind} (WT) - E_{bind} (mut).

This change in binding energy was compared to data from experimental (exptl) studies (Gulnik et al. (1995) Biochemistry 35:9282-9287, Klabe et al. (1998) Biochemistry 37:8735-8742, Pazhanisami et al. (1996) J. Biol. Chem. 271:17979-17985, Jacobsen et al. (1995) Virology 206:527-534, Maschera et al. (1996) J. Biol. Chem. 217:33231-33235) based on the equation:

 $\Delta E_{bind}(exptl) = RTIn(K_imut/K_iwt).$

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Plots of ΔE_{bind} (calculated) vs. ΔE_{bind} (exptl) were generated, and the results, summarized in Table 3, show a strong correlation between the calculated binding energies and the experimentally determined binding energies for the PR-inhibitor complexes. For example, the correlation coefficient R for PR-ritonavir and PR-amprenavir is 0.9, where R=1 denotes congruency between the computationally calculated and experimentally determined binding energy data. These correlation data validate the computational protocol and calculations described herein as a method for predicting protein-drug binding or protein-drug resistance (i.e. non-binding). The

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evaluation of changes in binding energy of protein-drug complexes upon protein sequence variations can be used as a possible descriptor and, thus, can be used to predict the efficacy of drugs on proteins resulting polymorphisms in genes. Moreover, the analysis of the free energy of binding in complexes between the protein models that are produced by the method set forth in this example and drugs that have been designed or modified is a good predictive tool for drug designers.

TABLE 3

Correlation between Experimental and Calculated Binding Energies
for HIV Protease Inhibitors

HIV PRInhibitor	X-ray Complex ID	No of exptl. data points	Correlation coefficient R	Correlation S.D., kcal/mol
Saquinavir	1HXB	18	0.84	0.68
Indinavir	1HSG	17	0.79	0.80
Ritonavir	1HXW	12	0.90	0.72
Amprenavir	1HPV	15	0.90	0.54
Nelfinavir	10HR	Insufficient data		

Identification of structural invariant regions of HIV Protease

Clinical effectiveness of HIV PR inhibitors is limited by the rapid emergence of drug-resistant mutations. Resistant PR variants first occur by the mutation of amino acids close to or in and around the drug binding site, which are then accompanied by compensatory mutations of more distant amino acids. The identification of highly conserved, structural invariant regions of a PR would provide new potential targets and thus lead to the development of therapeutics having greater clinical efficacy than those drugs commonly employed to treat HIV.

The protein sequences of HIV protease were obtained from GenBank and from the blood samples of patients using standard isolation and sequencing techniques well known in the arts. The protein sequences were modeled into 3-D structures using the computational

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protocol described in Example 1. The protease sequences were aligned, and the frequency of mutation, regardless of type, was determined at each amino acid position and plotted in Figure 7, where the frequency of mutation in this set of HIV-1 Protease sequences varied from 0 to 40%. Sequence alignment also revealed how many different types of amino acids could be substituted in any specific residue, yielding the tolerance of each residue to substitutions of different types. The data showing the frequency of mutation of each residue out of PR sequences, the types of mutations, and the distance of the mutating residue from the active site (Asp 28) are shown in FIG. 8. This information, sequences obtained from 10591 different genotypes, was used to identify invariant and/or highly conserved regions of PR and to map these regions to a 3-D structure for the purpose of identifying new potential regions on the protein as targets for therapeutic intervention. These invariant regions include, but are not limited to, residues 1-9, 25-29, 49-52, 78-81, and 94-99, where residue 1 is an aliphatic amino acid, more preferably proline; residue 2 is a hydrophilic amino acid, more preferably glutamine; residue 3 is an aliphatic amino acid, more preferably isoleucine; residue 4 is a hydrophilic amino acid, more preferably threonine; residue 5 is a hydrophobic amino acid, more preferably leucine; residue 6 is an aromatic amino acid, more preferably tryptophan; residue 7 is a hydrophilic amino acid, more preferably glutamine; residue 8 basic amino acid, more preferably arginine; residue 9 is an aliphatic amino acid, more preferably proline; residue 25 is a hydrophilic amino acid, more preferably aspartic acid; residue 26 is a hydrophilic amino acid, more preferably threonine; residue 27 is an aliphatic amino acid, more preferably glycine; residue 28 is an aliphatic amino acid, more preferably alanine; residue 29 is an acidic amino acid, more preferably aspartic acid; residue 49 is an aliphatic amino acid, more preferably glycine; residue 50 is a hydrophobic amino acid,

more preferably isoleucine; residue 51 is an aliphatic amino acid, more preferably glycine; residue 52 is an aliphatic amino acid, more preferably glycine; residue 78 is an aliphatic amino acid, more preferably glycine; residue 79 is an aliphatic amino acid, more preferably proline; residue 80 is a hydrophilic amino acid, more preferably threonine; residue 81 is an aliphatic amino acid, more preferably proline; residue 94 is an aliphatic amino acid, more preferably glycine; residue 95 is a thio-containing amino acid, more preferably cysteine; residue 96 is hydrophilic amino acid, more preferably threonine; residue 97 is hydrophobic amino acid, more preferably leucine; residue 98 is hydrophilic amino acid, more preferably asparagine; and residue 99 is an aromatic amino acid, more preferably phenylalanine. These invariant regions can subsequently be used to assist in the design drugs or therapeutic agents which bind to the invariant regions and disrupt the activity of the protease with greater efficacy than drugs commonly used to treat HIV and where the free energy of binding between said drug or therapeutic agent and the structural invariant region is evaluated as described herein. The methods described in this example can also be applied to HIV RT and to any protein of interest that exhibits polymorphisms.

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EXAMPLE 4

Computational Phenotyping of HIV-1 Protease and Reverse Transcriptase

Computational or *in silico* phenotyping is performed to assess phenotypic properties of a protein. This example demosntrates application of this method to HIV-1 protease and reverse transcriptase to test whether the efficacy of various protease inhibitors for an HIV patient.

To practice this method 3-D structures of HIV-1 protease and reverse transcriptase based upon the nucleic acid isolated from HIV from a patient are generated. Protein-drug binding analysis *in silico* in order to

-82-

determine whether drug binding does (i.e. sensitivity) or does not (i.e. resistance) take place.

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Sequencing of HIV-1 Protease and Reverse Transcriptase is performed on HIV-1 cDNA following extraction, reverse transcription, and PCR amplification of viral RNA obtained from patient specimens, such as blood samples or other body fluid or tissue samples. Methods for the extraction, reverse transcription, and PCR amplification of viral RNA are well known in the art. For each sequence, a computer-generated 3-D structure of the protein is modeled and then docked with antiviral drugs in silico using methods described in Example 1 and elsewhere herein to analyze protein-drug interactions. Antiviral drugs that can be tested include, but are not limited to, saquinavir, indinavir, ritonavir, amprenavir, and nelfinavir for HIV protease; zidovudine, lamivudine, stavudine, zalcitabine, didanosine, abacavir, adefovir, delavirdine, nevirapine, and efavirenz for HIV reverse transcriptase; and any FDA-approved or non-FDA approved antiviral drug. From these protein-drug interaction studies, relative drug resistance or sensitivity is inferred by calculating and evaluating the free energy of binding in low energy conformations of complexes between the variant protease structure and docked antiviral drug or variant reverse transcriptase structure and docked antiviral drug, using the methods described in Examples 1 and 3 and elsewhere herein.

The results of the computational phenotyping procedure can be presented as a patient report that states whether a drug or drugs are sensitive or resistant to the RT or PR obtained from the patient. Such a patient report assists physicians in selecting appropriate drugs for HIV patients. It also is useful for the *in vitro* diagnostics industry in an adjunct test/service capacity to help optimize antiviral therapy.

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EXAMPLE 5

HIV Protease and Reverse Transcriptase Databases

Exemplary databases of the 3-D protein structures of polymorphic variants are described in this example. The HIV PR and RT databases are a comprehensive collection of 3-D polymorphic structural data along with related information, including nucleic acids encoding all or a portion of the protein. These data provide a means to understand differences in the interactions between a drug or drugs and the structural variations of the drug targets.

This example describes the creation, interface for, and use of structural variant databases of HIV protease and reverse transcriptase polymorphic variants.

Construction of databases

To implement the RT or HIV database described herein, suitable 15 computer for performing database server tasks includes a "Pentium" level CPU having at least 128 MB of memory, 30 GB of disk storage, and 256 MB of disk swap space for files. A recommended configuration for better computer performance would include, for example, a "Pentium III" processor at 700 MHz or faster, memory of 256 MB or greater, disk storage space of 50 GB or more, and swap space of 500 MB or more. A suitable configuration for performing user tasks as described above includes a "Pentium" level CPU having 128 MB memory, disk space of 240 MB with swap space of 256 MB, and an optional display circuit card supporting OpenGL and having 4 MB of memory. A recommended configuration for better performance would include, for example, a "Pentium III" processor at 500 MHz or faster, memory of 256 MB or greater, disk space of 500 MB or more, swap space of 500 MB or more, and an optional display card having 8 MB of memory or more, supporting resolution of 1024 x 768.

Preferably, the software used in the computing system described above includes, for the server machine, operating system software such as "Windows NT Server 4.0" from Microsoft Corporation, with Service Pack 5, Version 1280 (10 June 1999) or more recent, with database management server software such as "Oracle Server Standard Edition 8.1" from Oracle Corporation, or better. The software used in a preferred embodiment of the user machine includes operating system software such as "Windows NT Workstation 4.0" from Microsoft Corporation, with Service Pack 5, version 1280 (10 June 1999) or more recent, as well as "Oracle Client Standard Edition Version 8.1" or better. The client machine will also be compliant with the "Java" programming language (Java Runtime Environment 1.2.2). As will be known to those skilled in the art, other configurations may be suitable, depending on the applications being used and the computer performance desired.

Database Interface

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The database interface was a Java-based interface with useful features. The database is interfaced to a molecular graphics package that includes 3-D visualization, including wire-frame representations; secondary structure ribbons; and solid surfaces, and structure analysis tools. The database also provides an interface to access all of the collected files from the same 3-D structure. The database interface also provides access to other databases, such as databases of chemical structures and public domain databases such as GenBank and the Protein Data Bank. The OpenGL and C++ module has real-time interaction with the sequence display and sequence analysis modules, such that highlighting residues in one display results in highlighting those same residues in other displays.

The relational database containing the protein information may be structured according to relational objects to facilitate the analysis and

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computation processes described in the preceding examples. FIG. 10 is a graphical representation of the database objects for the system described herein. The database is organized by classes, each of which is characterized by data attributes and subclasses for the proteins.

FIG. 10 shows that the database design includes classes comprising Variant and related classes of Sample, Residue, Model, Resistance_Entry, and Protein. Other classes include Conformation, Residue_Conformation, Atom, Drug, Family, and Subfamily. These classes store attribute data values and specify class parameters and behaviors to provide the functionality described herein.

For example, FIG. 10 shows that the Variant class stores parameters to specify a variant, including subclasses that specify a Variant_ID, Sample_ID, Protein_ID, Name, and Sequence, where Variant_ID is the identification number of the variant; Sample_ID is the identification number of the sample from which HIV PR and RT were obtained; Protein_ID is the identification number of the protein i.e. PR or RT; Name is the name of the variant distinguishing it from other variants encoded by the same DNA due to ambiguities in the nucleic acid sequence; and Sequence is the nucleotide or amino acid sequence. Similarly, FIG. 10 shows that the Sample class includes subclasses relating to a specific sample and which specify Sample_ID, Sample_Date, Sex, Ambiguity_Number, Distance, Sequence_Length, Sequence, Clade, and Region, where Sample_ID is as defined herein; Sample_Date is the date the sample was obtained; Sex is the gender of the sample donor; Ambiguity_Number is fraction of ambiguous nucleotide positions; Distance is a normalized number the variation of an amino acid from the master clade; Sequence_Length is the length of the sequence; Sequence is as defined herein; Clade is the master sequence; and Region is the geographic location from which the sample was obtained. The Model

-86-

class includes subclasses comprising Model_ID, Model_Name, Variant ID, and Drug ID, where Model ID is the identification number of the 3-D protein model; Model Name is the name of the 3-D protein model; Variant ID is as defined herein; and Drug_ID is the identification number of the drug i.e. antiviral drug. The atom class includes the subclasses comprising Atom_Name, Residue Conformation_ID, X Coordinate, Y Coordinate, and Z Coordinate, where Atom Name is the name of atom in the 3-D protein structure; Residue Conformation ID is the identification number of the amino acid conformation in a 3-D structure; and X Coordinate, Y Coordinate, and Z Coordinate are the coordinates of the 3-D protein structure. The conformation class includes the subclasses comprising Conformation ID, Model ID, and Refinement Level, where Conformation ID is the identification number of a conformation of a 3-D structure; Model ID is as defined herein, and Refinement Level is the number of times the conformation was refined energetically. The drug class includes the subclasses comprising Drug ID, Profile, Symbol, Name1, Name2, Company, and URL, where Drug ID is as defined herein; Symbol is the FDA symbol for the drug; Name1 is the name of the drug, Name2 is an alternative name of the drug; Company is the company that makes the drug; and URL is the website address of the company that makes the drug. The residue conformation class includes the subclasses comprising Residue_Conformation_ID, Conformation_ID, and Residue_ID, where Residue_Conformation_ID is as defined herein; Conformation_ID is as defined herein; and Residue_ID is the identification number of the amino acid. The Resistance Entry class includes the subclasses comprising Resistance_Entry ID, Profile, Protein ID, Residual Number, Amino Acid, Weight, and Maximum Weight, where Resistance Entry ID is; Protein_ID is as defined herein, Amino Acid is the amino acid. The Family class includes the subclasses comprising Family ID and

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Family_Name, where Family_ID is the identification number of the protein family and Family_Name is the name of the protein family. The SubFamily class includes the subclasses comprising SubFamily_ID, SubFamily_Name, and Family_ID, where SubFamily_ID is the identification number of the protein subfamily, SubFamily_Name is the name of the protein subfamily, and Family_ID is as defined herein. The Protein class includes the subclasses comprising Protein_ID, Protein_Name, Species, Multiple_Domain, Multiple_Chain, and Wild_Type, where Protein_ID is as defined herein, Protein_Name is the name of the protein i.e. RT or PR; Species is the species of the source of the protein i.e. humans; Multiple_Domain is the domain of the protein i.e p66 or p51 in the case of RT; Multiple_Chain is the a or b chain in the dimers of RT and PR; and Wild_Type is the wild-type protein sequence for RT and PR. The residue class includes the subclasses comprising Residue_ID, Variant_ID, Chain, Residue_Number, Insertion_Code, and Residue_Code, where Residue_ID is the identification number of the amino acid, Variant_ID is as defined herein, Chain, Residue_Number is the numbering of an amino acid in a protein sequence, Insertion_Code is the identification number if different insertions occur in the amino acid sequence, and Residue_Code is the single letter or 3-letter code of an amino acid. Those skilled in the art will understand the database design exemplified in FIG. 10. It should be understood that other classes or parameters may be included, as selected by those skilled in the art, for the desired database design.

Database Content

The databases contain information on the variants of HIV PR and RT present in patient populations. The master amino acid sequence, nucleic acid sequence, and 3-D structure are obtained from GenBank; an exemplary master sequence is set forth in SEQ ID No. 118. Nucleotide sequences exhibiting polymorphisms and the corresponding structural

variant protein sequences are determined by isolating nucleic from viruses and viral nucleic acid obtained from the blood samples of patients throughout the US, as well as from other countries, using sequencing methods well known in the art. The sequences were inputted into the RT and PR databases. Exemplary of the nucleotide sequences and the encoded amino acids for HIV RT and PR in this data base are set forth in SEQ ID NOS. 3 to 117, where r is g or a; y is t/u or c; m is a or c; k is g or t/u; s is g or c; w is a or t/u; b is g or c or t/u; d is a or g or t/u; h is a or c or t/u; v is a or g or c; and n is a or g or c or t/u or unknown or other. The amino acid sequences of the wild type and structural variants are used to create 3-D protein structures which are deposited into the databases.

1. 3-D Protein Models

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The structure of the wild-type or master sequence model of PR and RT were obtained from the crystal structures found in PDB. The initial structure was refined energetically using BPMC with an ECEPP force field as described in Example 1. The quality of the model was assessed by calculating Normalized Residue Energies (NREs), where models with e_{av} ≥ 1.5 require further energetic refinement; and models with $e_{av} < 1.5$ were deposited into the database as described herein. The 3-D protein structures of the variant sequences were generated by comparing these structures to the master sequence (see, e.g., SEQ ID No. 118; i.e., homology modeling) and energetically refining the models ab initio, using the same force field and BPMC procedure as the master sequence and applying the same quality control standard as described herein. Figure 11 is a tabulation of the 3-D coordinates of an exemplary HIV PR entry in a database that includes 3-D structures. For US purposes and where permitted, Tables 4 and 5 are provided electronically on CD ROM. These Tables house the coordinates that represent the 3-D protein structures of

proteins encoded by the nucleic acids set forth in SEQ. ID. NOS. 3-117. It will be noted that these sequences encode a full length PR and about 200 nucleotides the p51 subunit, which is the subunit of interest herein. To construct the full-length 3-D structure, the 3-D structure of each encoded portion of the p51 subunit was generated and then combined with the structure of the master sequence to produce a full-length structure.

These 3-D structures in the database can be selected and exported into computational docking programs for analyzing protein-drug interactions on known drugs, new drugs or modified drugs. The database 10 can be mined to find protein models that correspond to patients with a particular genetic polymorphism, patients with the most commonly occurring polymorphism, to a relevant patient subpopulation (e.g., gender, age, race, or other characteristic), to patients receiving a specific treatment regimen, to patients exhibiting a particular clinical response, to 15 structural invariants, or to other relevant criteria. Drugs can be docked into the active sites of PR and RT and subsequently energetically refined using an ECEPP force field and BPMC as described in Example 1. The quality control is that the protein-drug complex represents a low energy conformation, which may take several iterative 20 BMPC cycles. Then, the binding energies of the protein-drug complexes can be estimated using the methods of Example 1. Drug designers can modify the structures of drugs or design new drugs, using methods well known in the arts, to maximize the drug binding to the models generated by this database. 25

2. Other Data

Each PR or RT nucleotide sequence in the database has associated with it an identification number, the nucleotide sequence length, the translated amino acid sequence (or sequences in cases of ambiguous

-90-

nucleotide positions), a 3-D structure for each amino acid sequence (from which a number of structurally related values are calculated), the genotyping date, the gender of the patient, the geographical location from which the sample was sent, the clade of the sequence, the fraction of ambiguous nucleotide positions, drug information, and other clinical information.

Database Usage

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A query menu allows the user to retrieve data based on the various fields: sample ID, residue number (with or without specific amino acid mutation), date gender, geographic location, distance from the master sequence, and other useful queries. The set of sequences that satisfies the user's query are brought up in a sequence display module, which have variations from the master sequence indicated initially, although the sequences can be highlighted according to predicted resistance. This subset of sequences can be subjected to further analyses. For example, a histogram summarizing the number of mutations at each position in the subset can be generated. The 3-D structures for any of the variants in the database can be displayed and analyzed in the structure visualization module, allowing the user to compare the similarities and differences between 3-D structures by superimposing the 3-D structures. The user and also export these structures into programs for protein-binding studies as described herein. Thus, by mining the databases, a user will access 3-D structures and clinical and sample information that can be used in and correlated with protein-drug binding studies of HIV PR and RT.

Database Applications

The HIV PR and RT databases have many applications. The applications include, but are not limited to, any application and method provided herein, such as databases that assist in de novo drug design and drug binding calculations. In particular, the database can be used in the

design of 2nd and 3rd generation drugs to combat potential resistance to HIV therapy, and it can be used in the design of drugs that will impact a broad spectrum of the infected population. The databases provide the ability to design drugs that focus on the most highly conserved regions of a drug target and drugs that will avoid resistance to mutation. The database could be used to rank drug candidates by likely efficacy within a given subpopulation of patients (e.g. age, race, gender) in pre-clinical trials and to predict the most effective drug regimen to give a patient, and for designing clinical trials.

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Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

CLAIMS

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1. A computer-based method of drug design based on genetic polymorphisms, comprising:

obtaining more than one amino acid sequence of target proteins that are the product of a gene exhibiting genetic polymorphisms, wherein the sequences represent different genetic polymorphisms;

generating 3-dimensional (3-D) protein structural variant models from the sequences; and

based upon the structures of the 3-D models, designing drug

10 candidates, modifying existing drugs, identifying potential drug
candidates or identifying modifications of existing drugs based on
predicted intermolecular interactions of the drug candidates or modified
drugs with the structural variants.

2. The method of claim 1, wherein the structure-based drug design method comprises:

computationally docking the drug candidate or modified drug molecules with the target protein structural variant models;

energetically refining the docked complexes;

determining the binding interactions between the drug candidate or modified drug molecules and the structural variants; and

designing and identifying drugs or modifications to existing drugs based on the binding interactions.

- 3. The method of claim 2 wherein the binding interactions are determined by:
- calculating the free energy of binding between the protein structural variant model and the docked molecule; and

decomposing the total free energy of binding based on the interacting residues in the protein active site.

4. The method of claim 1 wherein:

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after the protein structural variant models derived from a particular genetic polymorphism are generated, selected model structures are analyzed to determine common structural features that are conserved throughout the selected models, wherein

the conserved structural features are used as a basis for structurebased drug design studies.

- 5. The method of claim 4, wherein the conserved structural features are stretches of non-contiguous residues, wherein each stretch contains at least two amino acids.
- 6. The method of claim 5, wherein the protein is human immunodeficiency virus protease.
- 7. The method of claim 6, wherein the conserved residues comprise residues comprise residues 1-9, 25-29, 49-52, 78-81 and 94-99; and wherein:

residue 1 is an aliphatic amino acid; residue 2 is a hydrophilic amino acid; residue 3 is an aliphatic amino acid; residue 4 is a hydrophilic amino acid; residue 5 is a hydrophobic amino acid; residue 6 is an aromatic amino acid; residue 7 is a hydrophilic amino acid; residue 8 is a basic amino acid; residue 9 is an aliphatic amino acid; residue 25 is an acidic amino acid; residue 26 is a hydrophobic amino acid; residue 27 is an aliphatic amino acid; residue 28 is an aliphatic amino acid; residue 29 is an acidic amino acid; residue 49 is an aliphatic amino acid; residue 50 is a hydrophobic amino acid; residue 51 is an aliphatic amino acid; residue 52 is an aliphatic amino acid; residue 78 is an aliphatic amino acid; residue 79 is an aliphatic amino acid; residue 80 is a hydrophilic amino acid; residue 95 is a thio-containing amino acid; residue 96 is a hydrophilic amino acid; residue 97 is hydrophobic amino acid; residue 98 is hydrophilic amino acid; and residue 99 is an aromatic amino acid.

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- 8. The method of claim 6, wherein the conserved residues comprise residues comprise residues 1-9, 25-29, 49-52, 78-81 and 94-99; and wherein:
- residue 1 is proline; residue 2 is glutamine; residue 3 is isoleucine; residue 4 is threonine; residue 5 is leucine; residue 6 is tryptophan; residue 7 is glutamine; residue 8 is arginine; residue 9 is proline; residue 25 is aspartic acid; residue 26 is threonine; residue 27 is glycine; residue 28 is alanine; residue 29 is aspartic acid; residue 49 is glycine; residue 50 is isoleucine; residue 51 is glycine; residue 52 is glycine; residue 78 is glycine; residue 79 is proline; residue 80 is threonine; residue 81 is proline; residue 94 is glycine; residue 95 is cysteine; residue 96 is threonine; residue 97 is leucine; residue 98 is asparagine; and residue 99 is phenylalanine.
- 9. The method of claim 6, wherein the HIV protease has the sequence of amino acids set forth in any of SEQ ID Nos. 3-74 and 77-117.
- 10. The method of claim 9, wherein the residues comprise residues 1-9, 25-29, 49-52, 78-81 and 94-99.
- 10. The method of claim 1, wherein the selected model structures represent the structural variants resulting from the most commonly occurring genetic polymorphisms.
- 11 The method of claim 1, wherein the selected model structures represent the structural variants resulting from genetic polymorphisms found in a selected patient subpopulation.
- 12. The method of claim 1 wherein the structural variant models25 are stored in a relational database, comprising:
 - 3-D molecular coordinates for the structural variants;
 - a molecular graphics interface for 3-D molecular structure visualization; computer functionality for protein sequence and structural analyses; and

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database searching tools.

- 13. The method of claim 12, wherein the database further comprises one or more of observed clinical data associated with the genetic polymorphisms, subject medical history and subject history.
 - 14. The method of claim 1, wherein:

after generating the 3-D protein structural variant models, the method comprises:

computationally docking drug molecules with the target protein models; and

- one energetically refining the docked complexes; and wherein the candidate drugs are specific for a protein with a selected polymorphism or specifically interact with all proteins exhibiting a polymorphism.
- 15. The method of claim 14, wherein the structure-based drug 15 design method comprises:

computationally docking drug or potential new drug candidate molecules with the target protein structural variant models;

energetically refining the docked complexes;

determining the binding interactions between the drug or potential new drug candidate molecules and the structural variants; and

designing potential new drugs or modifications to existing drugs based on the binding interactions.

- 16. The method of claim 15, wherein the binding interactions are determined by:
- 25 calculating the free energy of binding between the protein structural variant model and the docked molecule; and decomposing the total free energy of binding based on the interacting residues in the protein active site.
 - 17. The method of claim 14, wherein:

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after the protein structural variant models derived from a particular genetic polymorphism are generated, selected model structures are analyzed to determine common structural features that are conserved throughout the selected models; and

the conserved structural features are used as a basis for structurebased drug design studies.

- 18. The method of claim 17, wherein the selected model structures represent the structural variants resulting from the most commonly occurring genetic polymorphisms.
- 19. The method of claim 17, wherein the selected model structures represent the structural variants resulting from genetic polymorphisms found in a specific patient subpopulation.
 - 20. The method of claim 12, wherein the selected model structures represent structural variants derived from patients the receive a specific treatment regimen.
 - 21. The method of claim 12, wherein the selected model structures represent structural variants derived from patients that exhibit a particular clinical responses to a given drug.
- 22. The method of claim 12, wherein the selected model20 structures represent structural variants derived based on the duration of a particular drug treatment.
 - 23. The method of claim 12, wherein the structural variant models are stored in a relational database, comprising:
 - 3-D molecular coordinates for the structural variants;
- a molecular graphics interface for 3-D molecular structure visualization; and

functionality for protein sequence and structural analysis; and database searching tools.

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- 24. The method of claim 12, wherein the database further comprises observed clinical data associated with the genetic polymorphisms, subject medical history and subject history.
- 25. A computer-based method of selecting drug therapies for patients based on genetic polymorphisms, comprising:

obtaining amino acid sequences of a target protein that is the product of a gene exhibiting genetic polymorphisms, wherein the sequences represent different genetic polymorphisms;

generating 3-D protein structural variant models from the 10 sequences;

computationally docking drug molecules with the target protein models:

energetically refining the docked complexes;

determining the binding interactions between the drug or potential new drug candidate molecules and the models; and

selecting drug therapies based on the drug or drugs that have the most favorable binding interactions with the structural variant models.

- 26. The method of claim 25, wherein the binding interactions are determined by:
- calculating the free energy of binding between the protein structural variant and the docked drug molecule; and

decomposing the total free energy of binding based on the interacting residues in the protein active site.

- 27. The method of claim 1, further after generating the 3-D
 25 structural variant models, exporting some or all of them models into a program that computationally docks the models with test compounds to assess intermolecular interactions.
 - 28. A computer-based method for predicting clinical responses in patients based on genetic polymorphisms, comprising:

-98-

obtaining one or more amino acid sequences for a target protein that is the product of a gene exhibiting genetic polymorphisms;

generating 3-D protein structural variant models from the sequences;

building a relational database of protein structural variants derived based on genetic polymorphisms and observed clinical data associated with particular polymorphisms exhibited in the patients, wherein the database comprises:

3-D molecular coordinates for the structural variant models; a molecular graphics interface for 3-D molecular structure visualization;

computer functionality for protein sequence and structural analysis;

database searching tools; and

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observed clinical data associated with the genetic polymorphisms, subject medical history and subject history associated with the genetic polymorphisms;

obtaining a target protein structural variant based on the same gene associated with a polymorphism in a patient;

generating a 3-D protein model based on the subject's gene sequence;

screening/comparing the 3-D model derived from the subject to the structures contained in the database by:

identifying structures in the database that are similar to the model derived from the subject; and

predicting a clinical outcome for the patient based on the clinical data associated with the identified structures.

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29. A computer-based method for designing therapeutic agents that are active against biological targets that have become drug resistant due to genetic mutations, comprising:

obtaining a first 3-D protein structural variant model of a target protein against which a given drug has biological activity;

generating a second 3-D protein structural variant model of the target in which genetic mutations have occurred and against which the same drug is no longer biologically active;

comparing the structures of the first and second model to identify

10 structural differences; and

performing structure-based drug design calculations in order to identify new drugs or modifications to the existing drug to bring about biological activity against the second model.

30. A computer-based method for identifying compensatory mutations in a target protein, comprising:

obtaining the amino acid sequence of a target protein containing multiple amino acid mutations that is expressed in a patient, wherein the structure of a form of the target protein that responds to a particular drug, including the active site, has been structurally characterized;

generating a 3-D structural model of the mutated protein;

comparing the structure of the mutated protein with the form of the protein that responds to the drug to identify structural differences and/or similarities arising from the mutations;

comparing the biological activities of the drug against both the mutated protein and the form of the protein that responds to the drug to determine the effects of the mutations on drug response; and

identifying the mutations in the protein that affect biological activity based on the comparisons.

-100-

31. A method for creating a 3-D structural polymorphism relational database, comprising:

obtaining one or more amino acid sequences of a target protein that is the product of a gene exhibiting a genetic polymorphism, wherein sequences represent different genetic polymorphisms;

generating 3-D protein structural variant models from the sequences;

energetically refining the models;

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evaluating the quality of the models;

optionally obtaining associated clinical properties or data; and inputting the model and any associated properties and/or data into a relational database.

- 32. The method of claim 31, wherein after energetically refining the models, the models are further refined.
- 15 33. The method of claim 31, wherein the database comprises amino sequences of two or more polymorphic variants.
 - 34. The method of claim 31, wherein the database comprises amino sequences of ten or more polymorphic variants.
- 35. The method of claim 31, wherein the database comprises20 amino sequences of about 100 or more polymorphic variants .
 - 36. The method of claim 31, wherein the database comprises amino sequences of about 1000 or more polymorphic variants.
 - 37. The method of claim 31, wherein the database comprises amino sequences of more than 8000 polymorphic variants.
 - 38. A database created by the method of claim 31.
 - 39. The database of claim 38, comprising variant 3-dimensional structures of a selected target.
 - 40. The database of claim 38 that comprises structures of proteases or polymerases.

- 41. The database of claim 38, wherein the proteases are viral proteases or polymerases.
- 42. The database of claim 38, wherein the viral proteases are human immunodeficiency virus proteases and the polymerase is a viral reverse transcriptase.
- 43. The method of claim 31, wherein quality is assessed by computing the normalized residue energies such that if e_{av} is ≥ 1.5 a model is further refined until e_{av} is < 1.5; if e_{av} is < 1.5 a model is deposited into the database.
- 10 44. The method of claim 1, wherein the target is an enzyme.
 - 45. The method of claim 44, wherein the enzyme is a protease or polymerase.
 - 46. The method of claim 45, wherein the polymerase is a reverse transcriptase.
- 15 47. The method of claim 44, wherein the target is a protein expressed by an infectious agent.
 - 48. The method of claim 44, wherein the target is enzyme expressed by a an infectious agent.
- 49. The method of claim 48, wherein the agent is a human immunodeficiency virus (HIV).
 - 50. A computer system, comprising a database containing data representative of the three dimensional structure of polymorphic variants of a drug target.
- 51. The system of claim 50, wherein the target is a cell surface receptor or an enzyme.
 - 52. The system of claim 50, wherein the enzyme is a protease or a polymerase.
 - 53. A database, comprising:

-102-

sequences of nucleotides encoding a protein or portions thereof, wherein proteins comprise polymorphic variants; and the portions encode a domain of the protein that comprises a site in the protein that binds to a drug candidates; and

the coordinates of 3-dimensional (3-D) structures of the encoded proteins or portions thereof.

- 54. The database of claim 53 that is a relational database.
- 55. The database of claim 53 that comprises at least 2 polymorphic variants and the corresponding 3-D structures.

__ 5

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- 10 56. The database of claim 55 that comprises at more than 10, more than 100, more than 1000, more than 8000, or more than 10,000 polymorphic variants and the corresponding 3-D structures.
 - 57. The database of claim 53, wherein the protein is a receptor or enzyme from a eukaryotic or prokaryotic organism.
 - 58. The database of claim 53, wherein the organism is a pathogen or a mammal.
 - 59. The database of claim 53, wherein the organism is a pathogen is a virus or bacterium and the mammal is a human.
- 60. The database of claim 53, wherein the protein is a protease 20 or a reverse transcriptase.
 - 61. A database, comprising the sequences of nucleotides set forth in SEQ ID Nos. 3-117 that encode HIV protease or the portion of HIV reverse transcriptase set forth in each SEQ ID.
- 62. The database of claim 53, further comprising 3-D structural coordinates for a protein or portion thereof comprising sequences of amino acids encoded by each of SEQ ID Nos. 3-117.
 - 63. The database of claim 54, wherein the protein is HIV protease.

- 64. The database of claim 54, wherein the protein is HIV reverse transcriptase.
- 65. The method of claim 1, wherein the target protein is a eukaryotic or prokaryotic protein.
- 66. The method of claim 1, wherein the target protein is an animal protein, a plant protein or a protein from a pathogen.

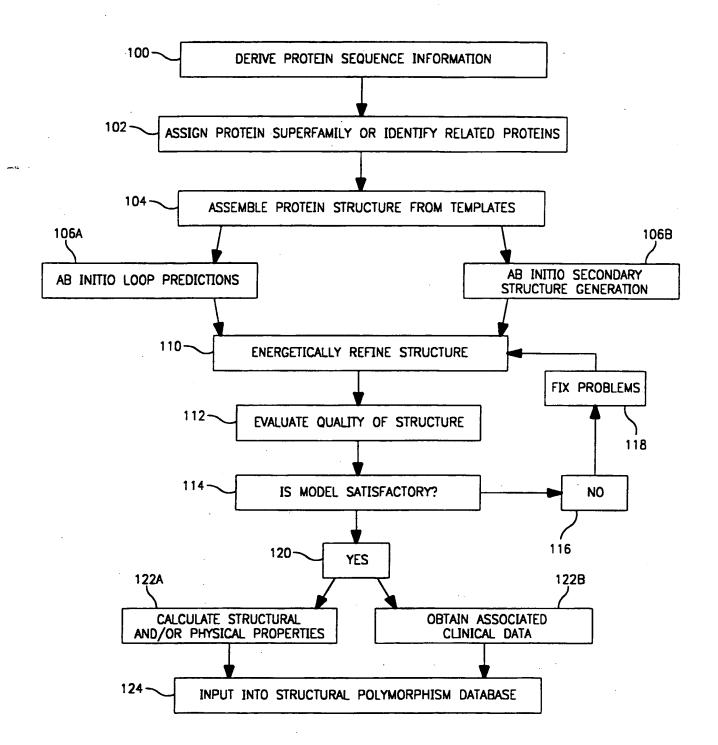


FIG. I

SUBSTITUTE SHEET (RULE 26)

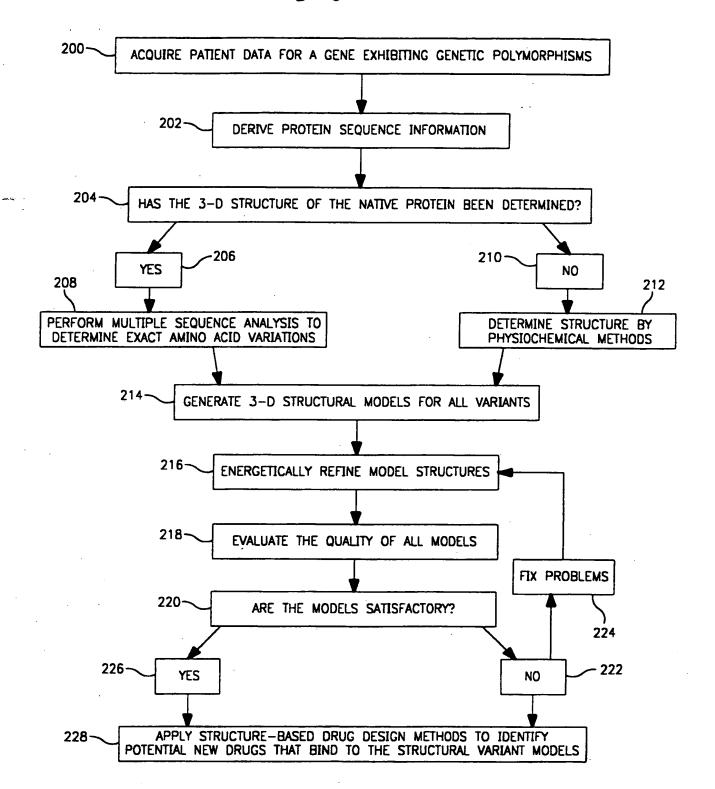


FIG. 2

SUBSTITUTE SHEET (RULE 26)

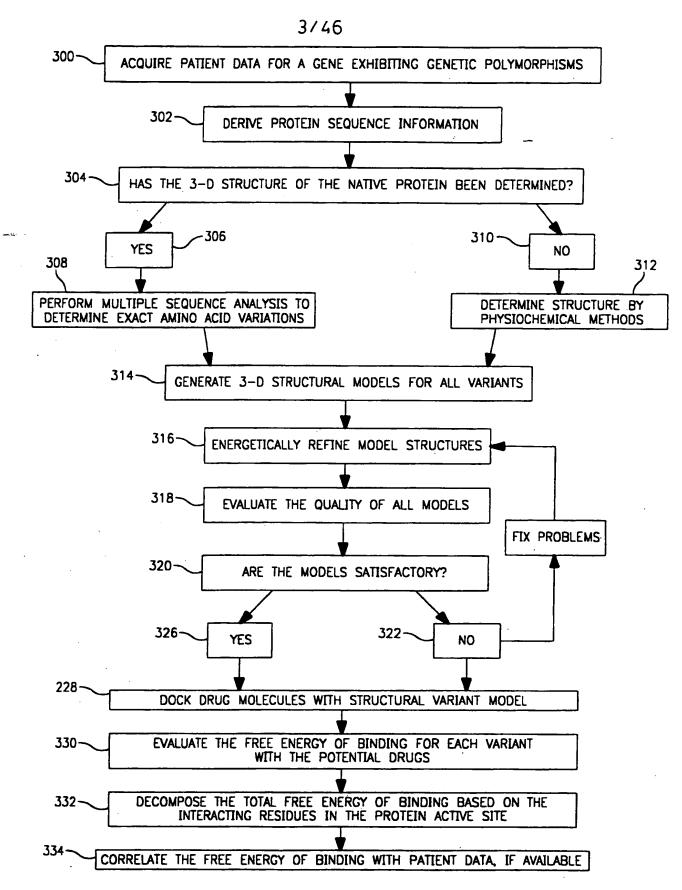
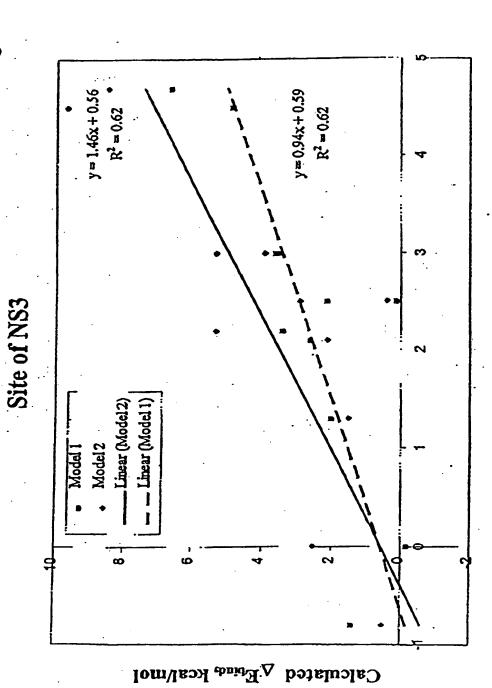


FIG. 3
SUBSTITUTE SHEET (RULE 26)

of Binding Energy upon Ligand Modifications in the Binding Correlation between Experimental and Calculated Changes F1G.



Expected AEbhas kcalmol

COMPARISON OF CALCULATED VERUS EXPERIMENTAL BINDING FREE ENERGY CHANGES

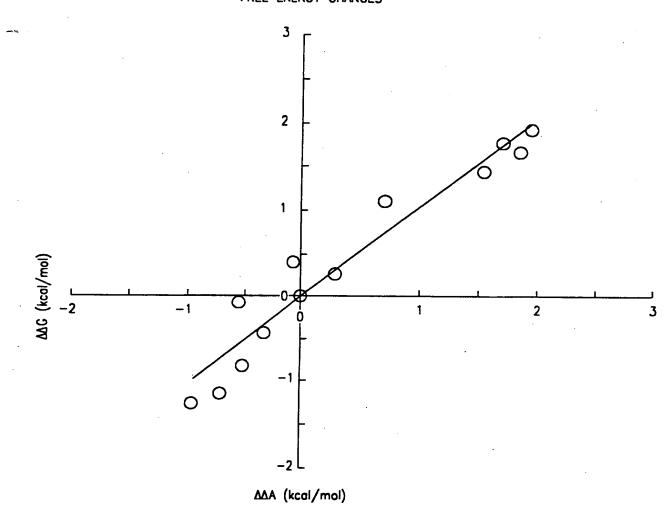
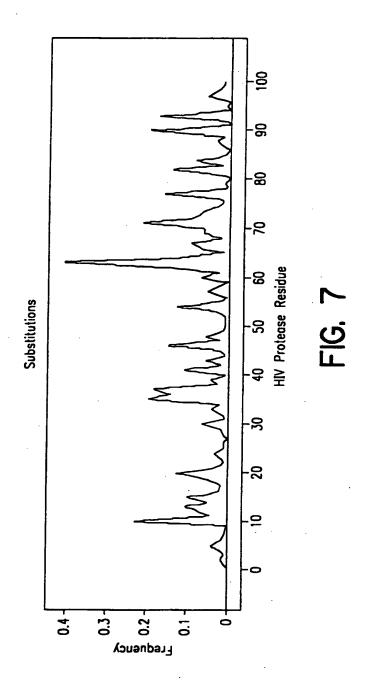


FIG. 5

HIV PROTEASE INHIBITORS APPROVED BY FDA

NH NH NH O S NH OH NH O S NH OH NH O S NH OH NH O S

FIG. 6



Database filename: hivpr.mdb Number of structures: 10591 Tolerance (%) >= 1.05

PecNum	TotOcc	TotFree	Dist	WtAA	Ni. com h de ch	\$441 :a4	NumList
1	11	•	15.4	Р	0	MULLISL	NumList
2	32	0					
			14.5	Q	0		
. 3	38	0	12.1	1	0		
4	106	0	13.0	T .	0		
5	100	0	11.3	L	0		
. 6	. 47		14.3	W	0		
7	58	0	12.8	Q	0		
8	27	0	9.6	R	0		
9	11	0	7.9	P	0		
10	4004	37.8	9.2	L	3	IV F	3162 441 278
11	82	0	10.9	· . V	0		
12	1117	10.5	13.7	T	5	SEPAN	241 185 158 155 117
13	1745	16.5	13.7	I	1	V	1717
14	646	6.1	17.0	K	1	R	623
15	1760	16.6	17.5	I	1	V	1709
16	361	3.4	20.9	G	1	Ε .	254
17	56	0	22.4	G	0.	•	
18	242	2.3	20.5	Q	0		
19	1340	12.7	18.3	L	4	IVQT	873 162 130 128
20	1549	14.6	15.4	K	4	IRTM	576 560 209 145
21	43	0	12.7	Ε	0		
22	46		9.0	A	0		•
23	89	0	5.8	L	0		
24	402	3.8	3.8	L	. 1	I	377

FIG. 8A

25	28	0	0.0	D	0		
26	· 14	0	3.8	T	0.		
27	9	0	5.5	G	0		
28	16	0	5.8	A	0	•	
29	34	0	8.7	D	0		
30	770	7.3	9.2	D	1	N	725
31	15	0	8.9	T	0		
32	238	2.2	10.5	V	1	1	221
33	578	5.5	12.4	Ľ	3	VIF	207 189 172
34	88	0	15.1	Ε	0	•	•
35	2790	26.3	18.6	Ε	1	D	2646
36	2780	. 26.2	20.2	М	2	IV	2549 129
37	3252	30.7	22.8	N	4	DSET	1253 1129 246 209
38	54	0	22.0	L	0		
39	302	2.9	24.9	Р	1	S	133
40	19	0	25.5	G	0		
41	2249	21.2	26.0	R	1 .	K ·	2235
42	21	0	23.5	W	0		
43	372	3.5	23.7	K	2	TR	166 144
44	12	0	22.6	Р	0		
45	208	2	20.0	K	1	R	170
46	2165	20.4	18.8	M	2	IL	1580 560
47	47	. 0	15.4	T	0		
48	445	4.2	14.9	G	1	, V	385
49	17	Ó	12.9	G	0		
50	31	0	14.5	I	0		•
51	24	0	17.6	G	0		
52	12	. 0	18.3	G	0		
53	408	3.9	18.1	F	1	L	360

FIG. 8B

54	1661	15.7	18.0	I	1	V	1460
55	164	1.5	19.7	K	1	R	149
56	13	0	18.1	٧	0		
57	1194	11.3	19.7	R	1	K	1162
58	341	3.2	18.6	Q	1	Ē	317
59	20	0	19.4	Y	0		
60	992	9.4	19.6	D	1	Ε	938
61	468	4.4	19.9	Q	1	E .	285
62	2711	25.6	18.6	1	1	V	2685
63	8864	83.7	18.5	L	6	PASTQH	7245 380 321 266 226 162
64	2238	21.1	15.8	I	2	V L	1931 223
65	222	2.1	15.6	Ε	1	D	206
66	194	1.8	12.8	I	0		·
67	309	2.9	14.6	С	1	S	143
68	51·	0	17.5	G	0		
69	773	7.3	16.1	Н	2	QY	376 206
70	478	4.5	17.0	K	1	R	359
71	3664	34.6	15.3	A	3	VTI	2301 1145 190
72	1494	14.1	17.2	1	3	VTL	650 409 126
73	1246	11.8	15.8	G	2	ST	932 185
74	658	6.2	15.4	T	2	SA	433 126
75	73	0	14.1	V	0		
76	59	0	14.6	L	0		
77	3533	33.4	16.1	٧	1	1	3513
78	. 8	0	16.9	G	0		
79	95	0	17.2	P	0		
80	6	0	13.6	T	0		
81	7	0	13.7	P	0		
82	2208	20.8	11.0	٧	2	AT	1668 284

FIG. 8C

07	44	0	9.7	N	0		
83					•	٧	1073
84	1091	10.3	6.3	I	•	•	
85	213	2	5.7	Ţ	1	V	198
86	16	0	5.3	G	0		,
87	32	0	7.3	R	0		
88	706	6.7	10.4	. N	2	DS	543 128
89	240	2.3	10.1	L	1	M	143
90	3429	32.4	8.3	L	1	М	3397
91	28	0	11.4	T	0		
92	227	2.1	13.6	Q	1	·K	169
93	3095	29.5	13.1	I	1	L	3041
94	15	0	13.6	G	0		
95	100	0	10.6	C	0		
96	6	0	11.2	T	0		•
97	83	0	10.7	L	0		
98	44	0	14.2	N	0		
99	35	0	16.4	F	0		

FIG. 8D

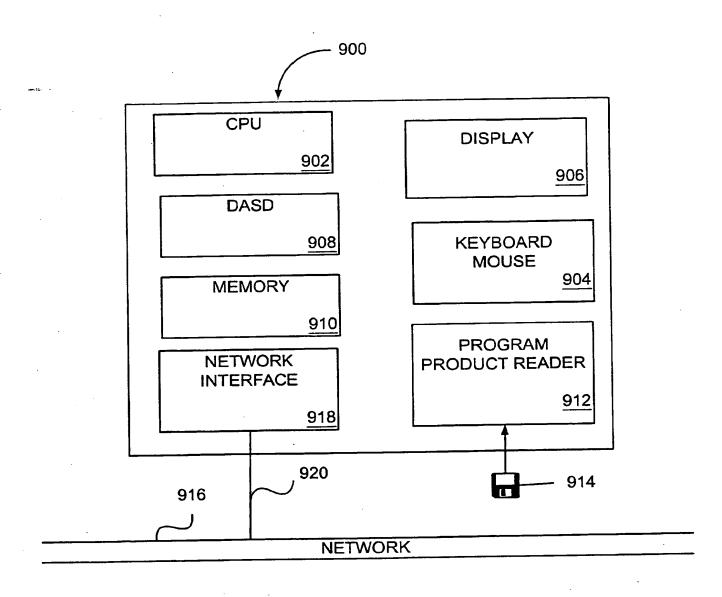
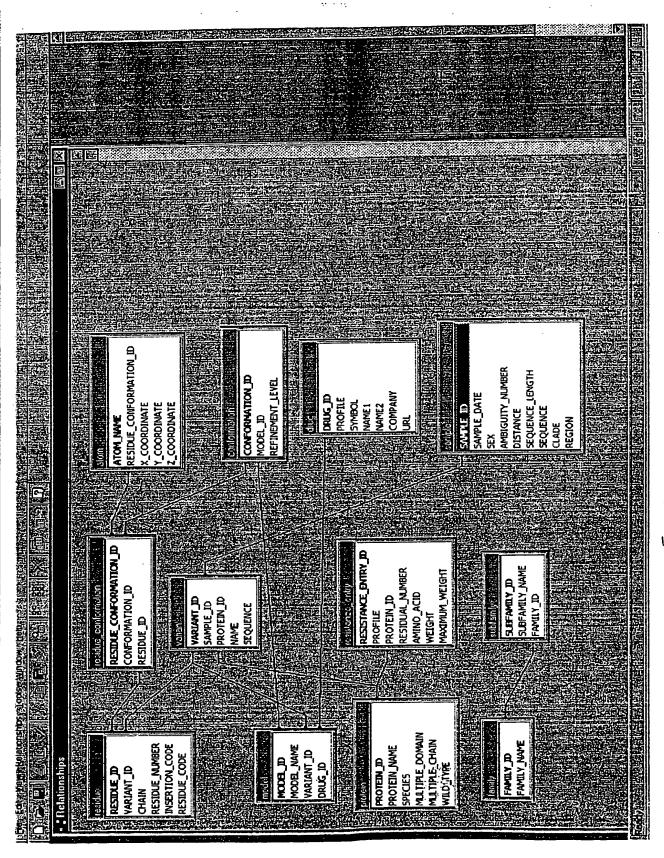


FIG. 9



			14	4/	46			
) TOY	1	N	PRO A		1	-3.433	7.956	34.152
ATOM	1 2	CA		A	ī	-2.653	6.918	34.784
MOTA	3	C		A	ī	-1.242	7.005	34.259
ATOM		0		A	ī	-0.950	7.638	33.216
ATOM	4	CB		A	ī	-3.281	5.601	34.262
ATOM	5	CG		A	ī	-4.191	5.995	33.118
ATOM	6 7	CD		A	ī	-4.547	7.451	33.339
ATOM		1H		A	ī	-2.845	8.493	33.547
ATOM		2H		A	ī	-3.824	8.552	34.853
ATOM	10	N	GLN .		2	-0.259	6.464	35.001
ATOM	11	H	GLN .		2	-0.475	6.057	35.889
ATOM	12	CA	GLN .		2	1.115	6.443	34.568
ATOM	13	C	GLN		2	1.452	4.993	34.301
ATOM	1:4	Õ		A	2	1.379	4.106	35.173
ATOM ATOM	15	CB		Α	2	2.070	6.966	35.653
ATOM	16	CG	GLN		2	3.549	6.859	35.240
ATOM	17	CD	GLN		2	4.490	7.744	36.054
ATOM	18	OE1	GLN		2	4.771	8.888	35.719
ATOM	19	NE2	GLN		2	4.980	7.190	37.144
ATOM	20	1HE2		Α	2	5.605	7.702	37.734
ATOM	21	2HE2	GLN		2	4.731	6.253	37.390
ATOM	22	N	ILE		3	1.784	4.644	33.037
ATOM	23	H		A	3	1.876	5.351	32.336
ATOM	24	CA		A	3	2.013	3.257	32.665
ATOM	25	C		A	3	3.505	3.028	32.473
ATOM	26	ŏ		A	3	4.242	3.777	31.787
ATOM	27	СВ		A	3.	1.226	2.944	31.370
ATOM	28	CG1		A	3	-0.274	3.239	31.603
ATOM	29	CG2		A	3	1.427	1.480	30.901
ATOM	30	CD1		Α	3	-1.089	3.219	30.322
ATOM	31	N	THR	Α	4	4.071	2.032	33.177
ATOM	32	H	THR		4	3.525	1.525	33.844
ATOM	33	CA	THR		4	5.451	1.661	33.007
ATOM	34	С	THR	Α	4	5.515	0.637	31.901
ATOM	35	0	THR	Α	4	4.490	0.143	31.397
ATOM	36	CB	THR	Α	4	6.051	1.125	34.324
ATOM	37	OG1	THR	Α	4	5.224	0.069	34.791
ATOM	38	HG1	THR	Α	4	5.589	-0.299	35.646
ATOM	39	CG2	THR	A	4	6.085	2.212	35.431
MOTA	40	N	LEU	Α	5	6.677	0.281	31.405
ATOM	41	H	LEU	Α	5	7.518	0.530	31.885
ATOM	42	CA	LEU	Α	5	6.754	-0.464	30.177 30.356
MOTA	43	С	LEU		5	7.432	-1.813	29.426
ATOM	44	0	LEU		5	7.940	-2.464	29.420
MOTA	45	CB	LEU	Α	5	7.459	0.394	28.775
MOTA	46	CG	LEU	Α	5	6.668	1.671	27.939
ATOM	47	CD1	LEU		5	7.493	2.649	28.099
ATOM	48	CD2			5	5.345	1.307	31.594
ATOM	49	N	TRP		6	7.420	-2.351	32.356
MOTA	50	H	TRP		6	7.030	-1.833	31.865
ATOM	51	CA	TRP		6	7.958	-3.669	31.204
ATOM	52	C	TRP		6	7.071	-4.697	30.828
MOTA	53	0	TRP		6	7.520	-5.798 -3.913	33.367
ATOM	54		TRP		. 6	8.099		34.070
MOTA	55	CG	TRP	Α	6	9.041	-2.974	54.070

FIG. 1 IA

	15 /	46			
		6	8.745		34.646
ATOM	56 CD1 TRP A 57 CD2 TRP A	6	10.449	• • •	34.273
MOTA		6	9.875		35.190
MOTA	JU	6	9.930	• •	35.668
ATOM	39 1102 221	6	10.932		34.974
ATOM	00 000	6	11.334		33.924
MOTA	61 653	6	12.257	-1.917	35.333
MOTA	·	6	12.650	-4.065	34.278
ATOM	3	6	13.106	-2.942	34.974
MOTA	04 0	7	5.773	-4.448	30.973
MOTA	05 1.	7	5.354	-3.619	31.343
ATOM	OT 17 3	7	4.952	-5.339	30.205
ATOM	67 CA GLN A 68 C GLN A	7	4.438	-4.569	29.033
ATOM	69 O GLN A	7	4.433	-3.321	29.000
ATOM	70 CB GLN A	7	3.712	-5.693	30.969
ATOM	71 CG GLN A	7	4.015	-6.467	32.210
ATOM	72 CD GLN A	7	2.734	-6.678	32.917
ATOM	73 OE1 GLN A	7	2.053	-7.681	32.712
ATOM	74 NE2 GLN A	7	2.356	-5.682	33.736
ATOM	75 1HE2 GLN A	7	1.501	-5.748	34.251
MOTA	76 2HE2 GLN A	7	2.926	-4.867	33.837
MOTA	77 N ARG A	8.	3.777	-5.239	28.078 28.142
ATOM ATOM	78 H ARG A	8	3.688	-6.233	26.142
ATOM	79 CA ARG A	8	3.183	-4.568	27.461
ATOM	80 C ARG A	8	2.117	-3.648	28.387
ATOM	81 O ARG A	8	1.333	-3.965	25.975
ATOM	82 CB ARG A	8	2.574	-5.555 -6.593	25.437
ATOM	83 CG ARG A	8	3.532	-6.533 -7.610	24.579
ATOM	84 CD ARG A	8	2.842	-8.487	23.900
ATOM	85 NE ARGA	8	3.787	-8.279	23.982
ATOM	86 HE ARG A	8	4.762 3.405	-9.541	23.185
ATOM	87 CZ ARG A	8	2.125	-9.871	23.052
ATOM	88 NH1 ARG A	8	1.418	-9.321	23.496
MOTA	89 2HH1 ARG A	8	1.869	-10.670	22.508
ATOM	90 1HH1 ARG A	8	4.332	-10.286	22.589
ATOM	91 NH2 ARG A	8	4.062	-11.082	22.048
ATOM	92 1HH2 ARG A	8	5.299	-10.050	22.682
MOTA	93 2HH2 ARG A	8	1.990	-2.428	26.938
MOTA	94 N PRO A	9 9	1.001	-1.462	27.440
MOTA	95 CA PRO A	9	-0.365	-1.697	26.821
MOTA	96 C PRO A	9	-0.918	-0.935	26.008
MOTA	97 O PRO A 98 CB PRO A	9	1.572	-0.112	27.041
MOTA	70 02 000	9	2.553	-0.404	25.931
MOTA		9	3.024	-1.820	26.084
MOTA	100 CD 200	10	-1.028	-2.803	27.227
ATOM	101	10	-0.616	-3.404	27.912
ATOM		10	-2.319	-3.143	26.698
MOTA	103 CA LEU A 104 C LEU A	10	-3.390	-2.565	27.591
ATOM	104 C EEU A	10	-3.336	-2.632	28.831
ATOM	106 CB LEU A	10	-2.451	-4.651	26.709
ATOM	107 CG LEU A	10	-1.483	-5.316	25.756
MOTA	108 CD1 LEU A	10	-1.159		26.212
ATOM	109 CD2 LEU A	10	-2.083		24.322
ATOM ATOM	110 N VAL A	11	-4.447	-1.952	27.033
MOTA	111 H VAL A	11	-4.507	-1.875	26.038
WIOL.	·				

FIG. I IB

	16/46			
	**** 3 11	J. J.		27.835 27.268
ATOM	112 021	• • • •		26.198
MOTA	113	0	2	27.897
MOTA	114 0 111	-5.420		28.551
MOTA	115 CB 11	-4.117		26.497
MOTA	110 001 111	-5.549	0.787 1.592	20.437
ATOM	117 CG2 VAL A 11 118 N THR A 12		1.592	28.868
ATOM	119 H THR A 12		1.141	27.496
ATOM	120 CA THR A 12		-0.726	26.795
ATOM ATOM	121 C THR A 12	-9.889 -9.856	0.436	27.247
ATOM	122 O THR A 12	-10.225	-2.385	28.659
ATOM	123 CB THR A 12		-3.458	29.338
ATOM	124 OG1 THR A 12		-3.766	30.096
MOTA	125 AG1 2110 3 12	-11.579	-2.895	28.156
MOTA	126 002 2223	-10.449	-0.932	25.594
MOTA	12/ N 222	-10.409	-1.841	25.178
MOTA	120 11 11111	-11.112	0.133	24.882 24.693
MOTA	129 CA 122 0		-0.292	24.833
ATOM	130 C ILE A 13 131 O ILE A 13		-1.469	23.511
MOTA	132 CB ILE A 13	-10.432	0.364 -0.896	22.628
MOTA	133 CG1 ILE A 13	-10.466	0.806	23.747
ATOM ATOM	134 CG2 ILE A 13	-8.986	-0.745	21.294
MOTA	135 CD1 ILE A 13	-9.755 -13.470	0.658	24.438
ATOM	136 N LYS A 14	-13.470	1.622	24.481
ATOM	137 H LYS A 14	-14.838	0.330	24.100
MOTA	138 CA LYS A 14	-15.088	0.877	22.719
MOTA	139 C 220	-14.859	2.059	22.375
MOTA	140 0 220 3 14	-15.855	0.916	25.099 24.864
ATOM	141 CB LYS A 14 142 CG LYS A 14	-17.325	0.518	26.166
MOTA MOTA	143 CD LYS A 14	-18.078	0.146 1.342	26.810
MOTA	144 CE LYS A 14	-18.826 -19.316	0.929	28.173
MOTA	145 NZ LYS A 14	-19.801	1.693	28.599
MOTA	146 1HZ LYS A 14	-18.536	0.670	28.743
MOTA	147 3HZ LYS A 14	-19.936	0.150	28.082
MOTA	140 2112 220	-15.535	0.005	21.798
MOTA	143 1 15	-15.806	-0.916	22.078 20.400
MOTA	150 H ILE A 15 151 CA ILE A 15	-15.642	0.347	19.887
MOTA	152 C ILE A 15	-16.894	-0.328 -1.542	20.041
MOTA MOTA	153 O ILE A 15	-17.115	-0.132	19.639
ATOM	154 CB ILE A 15	-14.382	0.148	18.125
ATOM	155 CG1 ILE A 15	-14.478 -14.082	-1.623	19.880
ATOM	156 CG2 ILE A 15	-14.237	1.603	17.796
MOTA	157 CD1 ILE A 15 158 N GLY A 16	-17.843	0.435	19.308
MOTA	150 1 51 3 16	-17.720	1.426	19.260
MOTA	109 11 024 3 16	-19.053	-0.143	18.745 19.789
MOTA	160 CA GLY A 16 161 C GLY A 16	-19.897	-0.817	19.516
ATOM	162 O GLY A 16	-20.774	-1.668 -0.493	21.088
MOTA MOTA	163 N GLY A 17	-19.712	0.204	21.334
ATOM	164 H GLY A 17	-19.038 -20.464	-1.126	22.160
ATOM	165 CA GLY A 17	-19.718	-2.335	22.653
MOTA	100 0 011 3 17	-20.147	-3.098	23.540
MOTA	167 O GLY A 17	. 10		

FIG. I IC

			1	7/46			
ATOM ATOM ATOM ATOM ATOM ATOM ATOM ATOM	168 169 170 171 172 173 174 175 176 177	H CA C O	GLN A	18 18 18 18 18 18 18 18	-18.507 -18.059 -17.806 -16.552 -15.887 -17.393 -16.911 -18.018 -19.131 -17.722 -18.404	-2.591 -1.900 -3.830 -3.549 -2.508 -4.294 -5.734 -6.728 -6.574 -7.773 -8.484	22.121 21.554 22.326 23.123 22.945 20.928 20.788 20.613 21.152 19.857 19.689 19.448
ATOM		2HE2	GLN A	18	-16.814 -16.133	-7.860 -4.397	24.087
MOTA	180	N	LEU A	19	-16.133	-5.202	24.312
MOTA	181	H	LEU A	19 19	-14.909	-4.178	24.808
ATOM	182	CA C	LEU A	19	-13.799	-4.912	24.090
MOTA MOTA	183 184	0	LEU A	19	-13.989	-6.018	23.558
ATOM	185	CB	LEU A	19	-14.982	-4.714	26.254
ATOM	186	CG	LEU A	19	-15.490	-3.778	27.374
ATOM	187	CD1	LEU A	19	-16.392	-2.639 -4.516	26.856 28.465
MOTA	188	CD2	LEU A	19	-16.208 -12.603	-4.316	23.978
MOTA	189	N	LYS A	20 20	-12.442	-3.448	24.324
MOTA	190	H	LYS A LYS A	20	-11.507	-5.082	23.365
ATOM	191 192	CA C	LYS A	20	-10.266	-4.618	24.062
MOTA MOTA	192	0	LYS A	20	-10.228	-3.611	24.816
MOTA	194	CB	LYS A	20	-11.397	-4.798	21.875
ATOM	195	CG	LYS A	20	-12.558	-5.356	21.100
ATOM	196	CD	LYS A	20	-12.537	-4.988 -5.958	19.615 18.827
ATOM	197	CE	LYS A	20	-13.414	-5.956 -7.208	18.639
MOTA	198	NZ	LYS A	20	-12.681 -13.247	-7.852	18.123
ATOM	199	1HZ	LYS A	20 20	-12.458	-7.601	19.531
ATOM	200	3HZ 2HZ	LYS A LYS A	20	-11.837	-7.027	18.134
ATOM	201 202	N	GLU A	21	-9.150	-5.357	23.893
MOTA MOTA	202	H	GLU A	21	-9.185	-6.188	23.338
MOTA	204	CA	GLU A	21	-7.890	-4.997	24.486
ATOM	205	C	GLU A	21	-7.001	-4.462	23.390 22.258
ATOM	206	0	GLU A	21	-6.970	-4.992	25.051
ATOM	207	CB	GLU A	21	-7.268 -5.835	-6.260 -6.140	25.480
MOTA	208	CG	GLU A	21	-5.405	-7.352	26.275
ATOM	209		GLU A	21 21	-5.624	-7.343	27.508
MOTA	210	OE1 OE2		21	-4.852	-8.309	25.684
ATOM ATOM	211 212	N	ALA A	22	-6.239	-3.369	23.595
MOTA	213	н	ALA A	22	-6.223	-2.938	24.497
ATOM	214	CA	ALA A	22	-5.419	-2.781	22.520 23.114
ATOM	215	С	ALA A	22	-4.138	-2.255	24.314
MOTA	216	0	ALA A	22	-3.985 6 134	-1.914 -1.657	21.821
MOTA	217	CB	ALA A	22	-6.134 -3.121	-2.091	22.240
MOTA	218	N	LEU A	23 23	-3.121	-2.236	21.263
ATOM	219	H	LEU A	23	-1.797	-1.712	22.640
ATOM	220 221	CA C	LEU A	23	-1.660	-0.230	22.443
MOTA" MOTA	221		LEU A	23	-2.020	0.349	21.402
ATOM	223	СВ	LEU A	23	-0.814	-2.486	21.732
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FIG. ID SUBSTITUTE SHEET (RULE 26)

18/46 -2.448 21.991 23 0.705 LEU A CG 224 MOTA 23.124 -3.400 1.088 23 CD1 LEU A 225 **ATOM** 20.708 -2.878 1.462 CD2 LEU A 23 226 MOTA 23.463 0.530 -1.192 24 LEU A 227 N MOTA 24.353 -1.015 0.110 LEU A 24 Н 228 MOTA 23.305 1.952 -0.935 LEU A 24 CA 229 ATOM 2.089 - 22.609 0.403 24 LEU A C 230 MOTA 23.130 1.717 1.471 LEU A 24 0 ATOM 231 24.681 -0.921 2.609 LEU A 24 CB 232 ATOM 25.477 -2.220 2.492 LEU A 24 CG 233 ATOM 26.772 3.291 -2.063 CD1 LEU A 24 234 ATOM 24.691 3.000 -3.419 CD2 LEU A 24 235 ATOM 21.397 2.590 0.454 ASP A 25 N 236 MOTA 3.085 21.032 -0.334 25 ASP A 237 Η MOTA 20.605 2.423 1.642 ASP A 25 CA 238 MOTA 20.059 3.750 2.130 ASP A 25 239 C MOTA 19.110 4.320 1.568 ASP A 25 0 240 ATOM 19.486 1.435 1.263 ASP A 25 CB 241 MOTA 18.561 1.051 2.428 ASP A 25 CG 242 ATOM 18.729 1.540 3.546 OD1 ASP A 25 243 MOTA 17.658 0.241 2.164 25 OD2 ASP A MOTA 244 20.605 4.337 3.203 26 THR A 245 N ATOM 21.346 3.880 3.694 26 THR A Н MOTA 246 20.144 5.652 3.691 26 THR A CA MOTA 247 5.583 18.778 4.397 THR A 26 C ATOM 248 18.079 6.587 4.642 26 THR A MOTA 249 0 6.219 21.217 4.596 26 THR A CB MOTA 250 21.386 5.324 5.716 OG1 THR A 26 MOTA 251 5.676 22.091 6.332 HG1 THR A 26 252 MOTA 22.577 6.320 3.878 CG2 THR A 26 253 MOTA 18.298 4.377 4.757 27 GLY A 254 N MOTA 18.811 3.550 4.526 27 GLY A Η **ATOM** 255 17.040 4.233 5.481 27 GLY A CA 256 MOTA 15.886 4.190 4.520 GLY A 27 С 257 MOTA 14.696 4.242 4.908 GLY A 27 0 258 ATOM 16.117 4.084 ALA A 3.197 28 259 N **ATOM** 17.057 4.091 2.856 ALA A 28 260 Н ATOM 15.018 3.955 2.213 ALA A 28 261 CA MOTA 14.750 5.299 1.598 ALA A 28 C **ATOM** 262 15.650 5.982 1.062 ALA A 28 263 0 MOTA 15.390 2.980 28 1.117 ALA A 264 CB ATOM 13.490 5.744 1.503 29 ASP A 265 N MOTA 12.746 5.216 1.912 29 ASP A 266 Н MOTA 13.213 0.810 6.984 29 ASP A ATOM 267 CA 6.724 13.327 -0.666 29 ASP A 268 C MOTA 13.568 7.637 -1.488 ASP A . 29 269 0 MOTA 11.775 7.433 1.009 ASP A 29 MOTA 270 CB 11.412 7.882 2.439 29 ASP A MOTA 271 CG 12.269 7.856 3.360 29 OD1 ASP A 272 MOTA 10.252 8.253 2.606 OD2 ASP A 29 273 ATOM 12.990 5.517 -1.14330 ASP A 274 N MOTA 12.800 4.769 -0.508 30 ASP A 275 Н ATOM 12.887 5.245 -2.57930 ASP A 276 CA ATOM 13.867 4.208 -3.057 ASP A 30 277 C MOTA 14.546 3.483 -2.284 ASP A 30 278 0 MOTA 11.456 4.758 -2.896 ASP A 30 279 CB ATOM

SUBSTITUTE SHEET (RULE 26)

19/46

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ATOM	280	CG ASP	Α	30	-2.495	5.768	10.425
MOTA	281		A	30	-3.067	6.871	10.423
ATOM	282	-	A	30	-1.596	5.494	9.618
	283		A	31	-4.393	4.076	14.002
ATOM	284		A	31	-5.004	4.700	13.515
MOTA			A	31	-5.059	3.062	14.829
MOTA	285		A	31	-5.565	1.967-	13.913
ATOM	286	O THR		31	-6.223	2.169	12.870
MOTA	287		A	31	-6.212	3.725	15.5 6 6
ATOM	288		A	31	-5.668	4.667	16.474
MOTA	289			31	-6.403	5.122	16.976
MOTA	290			31	-7.044	2.702	16.389
ATOM	291	CG2 THR	A	32	-5.187	0.713	14.235
MOTA	292	••		32	-4.649	0.555	15.063
ATOM	293		A	32	-5.517	-0.462	13.437
MOTA	294		A	32 32	-6.092	-1.506	14.365
MOTA	295	_	A		-5.502	-1.957	15.365
MOTA	296	O VAL		32	-4.260	-1.064	12.757
MOTA	297	CB VAL		32	-4.667	-2.136	11.735
MOTA	298		A	32	-3.422	0.017	12.032
ATOM	299	CG2 VAL		32		-1.923	14.119
MOTA	300	N LEU		33	-7.352 7.867	-1.523	13.361
MOTA	301	H LEU		33	-7.867	-2.940	14.929
ATOM	302	CA LEU		33	-7.982		14.107
MOTA	303	C LEU		33	-8.174	-4.203	12.853
ATOM	304	O LEU		33	-8.268	-4.247	15.408
ATOM	305	CB LEU		33	-9.336	-2.477	16.127
ATOM	306		Α	33	-9.292	-1.149	16.127
MOTA	307		Α	33	-10.710	-0.747	17.347
MOTA	308	CD2 LEU	Α	33	-8.348	-1.139	14.782
MOTA	309	N GLU	Α	34	-8.296	-5.319	14.782
ATOM	310	H GLU	Α	34	-8.244	-5.302	
ATOM	311	CA GLU	Α	34	-8.503	-6.551	14.086
ATOM	312	C GLU	Α	34	-9.909	-6.549	13.510
ATOM	313	O GLU	Α	34	-10.808	-5.717	13.795
ATOM	314	CB GLU	Α	34	-8.265	-7.750	15.010
ATOM	315	CG GLU	Α	34	-9.259	-7.791	16.165
ATOM	316	CD GLU	Α	34	-8.763	-8.552	17.404
ATOM	317	OE1 GLU	Α	34	-7.670	-9.193	17.368
MOTA	318	OE2 GLU	Α	34	-9.482	-8.497	18.407
ATOM	319	N GLU	Α	35	-10.152	-7.480	12.568
ATOM	320	H GLU	Α	35	-9.485	-8.208	12.407
ATOM	321	CA GLU	Α	35	-11.352	-7.466	11.773
ATOM	322	C GLU	Α	35	-12.631	-7.520	12.571
ATOM	323	O GLU	Α	35	-12.814	-8.294	13.528
ATOM	324	CB GLU	Α	35	-11.237	-8.536	10.707
ATOM	325	CG GLU		35	-9.945	-8.280	9.907
ATOM	326	CD GLU	Α	35	-9.872	-8.872	8.486
ATOM	327	OE1 GLU	A	35	-10.612	-8.401	7.603
ATOM	328	OE2 GLU		35	-9.024	-9.776	8.261
ATOM	329	N MET		36	-13.580	-6.598	12.278
ATOM	330	H MET		36	-13.439	-5.967	11.515
ATOM	331	CA MET		36	-14.819	-6.495	13.052
ATOM	332	C MET		36	-15.826	-5.635	12.271
ATOM	333	O MET		36	-15.514	-4.828	11.371
ATOM	334	CB MET	_	36	-14.593	-5.845	14.428
ATOM	335	CG MET		36	-14.279	-4.353	14.417
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FIG. I IF

				2	0/46			
ATOM	336	SD	MET	A	36	-14.251	-3.718	16.099
ATOM	337	CE		Α	36	-12.487	-3.846	16.409
ATOM	338	N	SER	Α	37	-17.130	-5.776	12.590
ATOM	339	Н	SER		37	-17.399	-6.431	13.296
ATOM	340	CA	SER	Α	37	-18.155	-5.005	11.940
ATOM	341	C		Α	37	-18.286	-3.693	12.657
ATOM	342	ō	SER		37	-18.593	-3.624	
ATOM	343	CB	SER		37	-19.506	-5.688	12.032
ATOM	344	OG	SER	Α	37	-19.455	-7.054	11.716
ATOM	345	HG	SER	Α	37	-20.367	-7.457	11.791
ATOM	346	N	LEU	Α	38	-18.185	-2.569	11.933
ATOM	347	H	LEU	Α	38	-17.956	-2.625	10.952
ATOM	348	CA	LEU	Α	38	-18.557	-1.247	12.465
ATOM	349	С	LEU	Α	38	-19.630	-0.605	11.572
MOTA	35:0	0	LEU	Α	38	-19.706	-0.939	10.391
MOTA	351	CB	LEU	Α	38	-17.315	-0.346	12.588
ATOM	352	CG		Α	38	-16.246	-0.818	13.596
ATOM	353	CD1		Α	38	-14.998	0.073	13.489
ATOM	354	CD2	LEU	Α	38	-16.756	-0.787	15.046
MOTA	355	N		Α	39	-20.455	0.321	12.108
MOTA	356	CA	PRO		39	-21.460	1.053	11.339
MOTA	357	С		Α	39	-20.824	2.176	10.502
MOTA	358	0	PRO		39	-19.654	2.519	10.685 12.389
ATOM	359	CB		Α	39	-22.430	1.607	13.600
ATOM	360	CG		A	39	-21.531	1.845	13.500
ATOM	361	CD	PRO		39	-20.539	0.686	9.586
MOTA	362	N	GLY		40	-21.620	2.749 2.417	9.493
ATOM	363	H	GLY		40	-22.569	3.811	8.678
ATOM	364	CA	GLY		40	-21.203	3.262	7.298
MOTA	365	C	GLY		40	-20.836 -21.405	2.268	6.845
ATOM	366	0	GLY		40	-19.895	3.945	6.631
ATOM	367	N		A	41 41	-19.496	4.761	7.071
ATOM	368	H	LYS	A A	41	-19.323	3.558	5.343
ATOM	369	CA C	LYS LYS	A	41	-17.798	3.757	5.371
ATOM ATOM	370 371	0	LYS	A	41	-17.263	4.462	6.229
ATOM	372	CB	LYS	A	41	-20.025	4.352	4.224
MOTA	372	CG	LYS		41	-19.703	3.839	2.810
ATOM	374	CD	LYS		41	-20.610	4.486	1.757
ATOM	375	CE	LYS		41	-20.240	3.964	0.366
ATOM	376	NZ		A	41	-21.097	4.552	-0.678
ATOM	377	1HZ		Α	41	-20.824	4.189	-1.580
ATOM	378	3HZ		Α	41	-20.993	5.556	-0.673
MOTA	379	2HZ	LYS	A	41	-22.061	4.311	-0.498
ATOM	380	N	TRP	Α	42	-17.104	3.091	4.439
ATOM	381		TRP	Α	42	-17.620	2.548	3.762
ATOM	382	CA	TRP	Α	42	-15.654	2.932	4.423
MOTA	383	С	TRP	A	42	-15.105	2.852	2.994
ATOM	384	0	TRP	Α	42	-15.845	2.702	2.021
ATOM	385	CB	TRP		42	-15.279	1.675	5.236
MOTA	386	CG	TRP		42	-16.214	0.514	5.094
MOTA	387	CD1	TRP		42	-16.230	-0.402	4.101
MOTA	388	CD2	TRP		42	-17.355	0.203	5.942
MOTA	389	NE1	TRP		42	-17.297	-1.260	4.281
MOTA	390	HE1	TRP		42	-17.504	-2.015	3.644
ATOM	391	CE2	TRP	Α	42	-18.045	-0.914	5.389

FIG. I IG SUBSTITUTE SHEET (RULE 26)

21/46	5
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						- 004	0 702	7.103
ATOM	392	CE3	TRP A	A	42	-17.896	0.792	
MOTA	393	CZ2	TRP A	Ą	42	-19.224	-1.421	5.959
ATOM	394	CZ3	TRP A	A	42	-19.077	0.298	7.675
ATOM	395		TRP A	A	42	-19.741	-0.806	7.112
ATOM	396	N		A	43	-13.771	2.932	2.911
	397	Н		A	43	-13.260	3.058	3.773
ATOM				A	43	-12.951	2.802	1.713
ATOM	398	CA		A.	43	-11.773	1.859	2.012
ATOM	399			A.	43	-11.359	1.760	3.166
MOTA	400	0			43	-12.451	4.193	1.270
MOTA	401	CB		A		-11.724	4.979	2.383
MOTA	402	CG	LYS A		43	-11.724	6.267	1.873
MOTA	403	CD	LYS		43	-9.784	6.001	1.065
MOTA	404	CE		A	43		5.458	1.903
ATOM	405	NZ		A.	43	-8.700	5.315	1.338
MOTA	40,6	1HZ		A	43	-7.876		2.300
MOTA	407	3HZ		A	43	-8.993	4.576	2.647
MOTA	408	2HZ	LYS .	A	43	-8.493	6.108	1.004
MOTA	409	N	PRO .	A	44	-11.177	1.197	
MOTA	410	CA	PRO .	Α	44	-9.947	0.435	1.187
ATOM	411	С	PRO .	Α	44	-8.760	1.392	1.379
ATOM	412	0	PRO .	Α	44	-8.711	2.434	0.720
ATOM	413	CB	PRO .	Α	44	-9.808	-0.393	-0.095
ATOM	414	CG	PRO .		44	-10.501	0.458	-1.159
ATOM	415	CD	PRO .		44	-11.630	1.132	-0.380
MOTA	416	N		Α	45	-7.790	1.030	2.240
ATOM	417	Н	LYS		45	-7.912	0.227	2.824
MOTA	418	CA	LYS		45	-6.547	1.747	2.314
MOTA	419	C.	LYS		45	-5.493	0.683	2.507
ATOM	420	o		A	45	-5.780	-0.470	2.869
	421	СВ		A	45	-6.594	2.699	3.524
MOTA	4.22	CG		A	45	-5.463	3.744	3.609
ATOM	423	CD		A	45	-5.340	4.289	5.052
MOTA		CE		A	45	-4.262	5.383	5.204
ATOM	424			A	45	-2.907	4.911	4.916
MOTA	425	NZ		A	45	-2.260	5.664	5.032
ATOM	426	1HZ			45	-2.864	4.577	3.975
ATOM	427	3HZ		A	45	-2.672	4.169	5.544
ATOM	428	2HZ		A	46	-4.224	0.949	2.193
MOTA	429	N		A		-3.998	1.805	1.728
ATOM	430	H		Α	46	-3.157	0.027	2.509
MOTA	431	CA	MET		46	-2.417	0.701	3.627
MOTA	432	C	MET		46	-2.259	1.937	3.634
MOTA	433	0	MET		46		-0.088	1.379
MOTA	434	CB	MET		46	-2.166	-0.366	0.053
MOTA	435	CG	MET		46	-2.782	-2.108	-0.118
MOTA	436	SD	MET		46	-3.076		-0.186
MOTA	437	CE	MET		46	-1.417	-2.652	4.586
MOTA	438	N	ILE		47	-1.827	-0.016	4.655
MOTA	439	. H	ILE		47	-2.010	-0.997	5.539
ATOM	440	CA	ILE		47	-0.922	0.586	
ATOM	441	C	ILE		47	0.233	-0.372	5.654
MOTA	442	0	ILE	A	47	0.135	-1.584	5.356
ATOM	443	CB	ILE	Α	47	-1.550	0.836	6.923
ATOM	444	CG1	ILE	Α	47	-2.459	-0.301	7.354
ATOM	445	CG2	ILE	A	47	-2.248	2.164	6.995
ATOM	446	CD1	ILE		47	-1.724	-1.336	8.111
ATOM	447	N	GLY	A	48	1.420	0.089	6.043

FIG. 1 IH SUBSTITUTE SHEET (RULE 26)

				2	2/46				
3.0004	4.40	**	GLY		48		1.509	1.040	6.339
ATOM	448	H CA	GLY		48		2.584	-0.753	6.048
ATOM	449	CA	GLY		48		3.280	-0.657	7.376
ATOM	450 451	0	GLY		48		3.050	0.190	8.265
ATOM	451	N	GLY		49		4.197	-1.617	7.603
MOTA	452	H	GLY		49		4.375	-2.308	6.902
MOTA	453	CA	GLY		49		4.936	-1.684	8.828
ATOM .	455	C	GLY		49		6.105	-2.589	8.533
ATOM	456	Ö	GLY		49		6.482	-2.807	7.370
ATOM	457	N	ILE		50		6.761	-3.173	9.552
ATOM	458	Н	ILE		50		6.552	-2.908	10.493
ATOM	459	CA	ILE		50		7.772	-4.184	9.344
ATOM	460	C	ILE	Α	50		7.148	-5.317	8.566
ATOM	461	0	ILE	A	50		5.981	-5.734	8.772
ATOM	462	CB	ILE	Α	50		8.258	-4.686	10.722
MOTA	463	CG1	ILE	Α	50		9.257	-3.714	11.382
ATOM	464	CG2		Α	50		8.813	-6.134	10.693 10.628
ATOM	465	CD1		Α	50		10.580	-3.498	7.596
ATOM	466	N	GLY		51		7.847	-5.891	7.395
MOTA	467	H	GLY		51		8.772	-5.569	6.850
ATOM	468	CA	GLY		51		7.265	-6.966	5.591
ATOM	469	С	GLY		51		6.519	-6.559	4.634
ATOM	470	0	GLY		51		6.430	-7.318 -5.375	5.517
ATOM	471	N	GLY		52		5.886	-3.373 -4.710	6.257
ATOM	472	H	GLY		52		5.990 5.108	-5.227	4.320
ATOM	473	CA	GLY		52 53		3.832	-4.415	4.516
ATOM	474	C	GLY		52 52		3.654	-3.624	5.467
ATOM	475	0	GLY		52 53		2.886	-4.518	3.559
ATOM	476	N		A A	53 53		3.013	-5.161	2.804
MOTA	477	H	PHE PHE	A	53 53		1.653	-3.720	3.566
ATOM	478 479	CA C		A	53		0.494	-4.651	3.783
ATOM ATOM	480	0		A	53		0.448	-5.816	3.336
ATOM	481	CB		A	53		1.424	-3.022	2.221
ATOM	482	CG		A	53		2.363	-1.896	2.008
ATOM	483	CD1		A	53		3.615	-2.135	1.447
ATOM	484	CD2		Α	53		2.011	-0.608	2.414
ATOM	485	CE1	PHE	Α	53		4.514	-1.087	1.275
ATOM	486	CE2	PHE	A	53		2.925	0.446	2.237
ATOM	487	CZ	PHE	Α	53		4.172	0.202	1.668
ATOM	488	N	ILE		54	•	-0.554	-4.173	4.439 4.895
ATOM	489	H	ILE		54		-0.491	-3.285	4.509
ATOM	490	CA	ILE		54		-1.789	-4.911	4.033
ATOM	491	C	ILE		54		-2.903	-3.995	3.855
MOTA	492	0	ILE		54		-2.751	-2.770	5.904
MOTA	493	CB	ILE		54		-2.034 -2.343	-5.535	6.988
ATOM	494	CG1	ILE		54			-4.481 -6.318	6.314
ATOM	495	CG2	ILE		54 54	•	-0.799 -3.010	-5.089	8.246
ATOM	496	CD1	ILE		54 55		-4.029	-4.577	3.560
MOTA	497	N	LYS		55 55		-4.023	-5.574	3.501
MOTA	498	H	LYS		55 55		-5.177	-3.798	3.129
ATOM	499	CA C	LYS LYS		55 55		-6.115	-3.726	4.300
ATOM	500	0	LYS		55		-6.422	-4.707	5.023
ATOM ATOM	501 502	CB	LYS		55		-5.928	-4.461	1.938
ATOM	503	CG	LYS		55		-6.853	-3.547	1,106
MION	503								

FIG. I II

23/46

						2 267	-3.332	1.714
MOTA	504	CD	LYS		55	-8.267		1.301
MOTA	505	CE	LYS	Α	55	-9.303	-4.392	
ATOM	506	NZ	LYS	Α	55	-10.521	-4.453	2.192
MOTA	507	1HZ	LYS	Α	55	-11.142	-5.162	1.859
ATOM	508	3HZ	LYS	Α	55	-10.987	-3.569	2.180
ATOM	509	2HZ	LYS	Α	55	-10.240	-4.669	3.127
ATOM	510	N	VAL		56	-6.599	-2.509	4.619
	511	H	VAL		56	-6.337	-1.713	4.073
ATOM	512	CA	VAL		56	-7.494	-2.311	5.735
ATOM		C	VAL		56	-8.711	-1.584	5.236
MOTA	513		VAL		56	-8.767	-1.029	4.114
MOTA	514	0	VAL		56	-6.759	-1.475	6.812
MOTA	515	CB				-5.569	-2.209	7.385
MOTA	516	CG1	VAL		56	-6.287	-0.108	6.268
MOTA	517	CG2	VAL		56		-1.539	6.005
ATOM	518	N	ARG		57	-9.784	-2.117	6.819
MOTA	519	H	ARG		57	-9.835		5.638
MOTA	520	CA	ARG	Α	57	-10.855	-0.648	
MOTA	521	С	ARG	A,	57	-10.738	0.534	6.554
MOTA	522	0	ARG	Α	57	-10.558	0.449	7.789
ATOM	523	CB	ARG	Α	57	-12.219	-1.271	5.835
ATOM	524	CG	ARG	Α	57	-12.480	-2.452	4.952
ATOM	525	CD	ARG	Α	57	-13.834	-3.051	5.195
ATOM	526	NE	ARG		57	-14.122	-4.137	4.270
ATOM	527	HE	ARG		57	13.442	-4.347	3.568
ATOM	528	CZ	ARG		5 7	-15.243	-4.851	4.324
ATOM	529	NH1	ARG		57	-16.175	-4.624	5.243
ATOM	530	2HH1	ARG		57	-16.044	-3.899	5.920
ATOM	531	1HH1	ARG		57	-17.008	-5.178	5.258
ATOM	532	NH2	ARG		57	-15.433	-5.822	3.434
ATOM	533	1HH2	ARG		57	-16.270	-6.368	3.461
ATOM	534	2HH2	ARG		57	-14.738	-6.006	2.738
ATOM	535	N	GLN		58	-10.881	1.741	6.036
ATOM	536	Н	GLN		58	-11.030	1.844	5.053
ATOM	537	CA	GLN		58	-10.830	2.922	6.839
ATOM	538	C	GLN		58	-12.231	3.342	7.205
	539	0	GLN		58	-13.106	3.608	6.359
ATOM	540	CB	GLN		58	-10.208	4.038	6.030
ATOM		CG	GLN		58	-10.055	5.293	6.817
ATOM	541		GLN		58	-9.632	6.411	5.927
MOTA	542	CD	GLN		58	-10.379	7.334	5.662
ATOM	543	OE1	GLN		58	-8.412	6.303	5.437
MOTA	544	NE2			58	-8.047	7.009	4.830
ATOM	545	1HE2	GLN		58	-7.843	5.514	5.668
ATOM	546	2HE2	GLN		59	-12.527	3.516	8.509
ATOM	547	N	TYR			-11.877	3.219	9.209
MOTA	548	H	TYR		59	-13.769	4.125	8.933
ATOM	549	CA	TYR		59	-13.411	5.452	9.565
MOTA	550	C	TYR		59	-12.416	5.592	10.310
ATOM	551	0	TYR		59		3.252	9.957
MOTA	552	CB	TYR		59	-14.517 -14.287	1.770	9.723
MOTA	553	CG	TYR		59			9.457
MOTA	554	CD1			59	-13.007	1.269	9.766
MOTA	555	CD2			59	-15.346	0.865	9.240
ATOM	556	CE1			- 59	-12.797	-0.092	9.240
MOTA	557	CE2			59	-15.148	-0.494	
ATOM	558	CZ	TYR		59	-13.873	-0.972	9.287 9.079
ATOM	559	OH	TYR	A	59	-13.721	-2.311	3.013

FIG. 1 J SUBSTITUTE SHEET (RULE 26)

PCT/US00/30863

				24	146				
	560	****	TYR	2 - A	59		-14.606	-2.771	9.154
MOTA	560 561	HH N		A	60		-14.151	6.542	9.300
ATOM ATOM	562	Н		A	60		-14.954	6.464	8.709
ATOM	563	CA		A	60		-13.822	7.836	9.846
ATOM	564	C		Α	60		-14.782	8.226	10.947
ATOM	565	0	ASP	Α	60		-15.941	7.765	11.053 8.769
ATOM	566	CB	ASP	A	60		-13.861	8.942	7.725
ATOM	567	CG		Α	60		-12.735	8.830 8.874	8.075
ATOM	568	OD1	-	A	60		-11.545 -13.060	8.702	
MOTA	569	OD2		A	60		-14.339	9.154	11.833
ATOM	570	N		A	61 61		-13.385	9.451	11.804
MOTA	571 571	H CA		A A	61		-15.151	9.804	12.885
ATOM	572 573	CA		A	61		-15.839	8.803	13.802
MOTA	574	0	GLN		61		-17.008	8.893	14.229
ATOM ATOM	575	CB	GLN		61		-16.097	10.908	12.338
ATOM	576	CG		A	61		-16.239	12.133	13.262
ATOM	577	CD		A	61		-16.910	13.366	12.629
ATOM	578	OE1		Α	61		-16.509	13.854	11.586
ATOM	579	NE2	GLN	Α	61		-17.937	13.887	13.292
ATOM	580	1HE2	GLN	Α	61		-18.416	14.689	12.934
MOTA	581	2HE2		Α	61		-18.239	13.482	14.155 14.175
MOTA	582	N		Α	62		-15.060	7.760 7.714	13.862
ATOM	583	H		A	62		-14.111	6.705	15.015
MOTA	584	CA		A	62		-15.557 -15.251	7.057	16.447
ATOM	585	C		A	62		-14.198	7.613	16.837
ATOM	586	O		A A	62 62		-14.829	5.397	14.653
ATOM	587	CB		A	62		-15.253	4.966	13.258
ATOM	588 589	CG1 CG2		A	62		-15.106	4.271	15.675
ATOM ATOM	590	CD1	ILE		62		-16.779	4.788	13.116
ATOM	591	N		A	63		-16.242	6.807	17.320
ATOM	592	H		Α	63		-17.089	6.383	17.000
ATOM	593	CA	LEU	Α	63		-16.127	7.131	18.719
ATOM	594	C	LEU	A	63		-15.518	5.942	19.425
ATOM	595	. 0	LEU		63		-15.869	4.753	19.269 19.282
MOTA	596	CB	LEU	A	63		-17.512	7.428	20.813
ATOM	597	CG	LEU		63		-17.660	7.598 8.632	21.404
MOTA	598	CD1			63		-16.711 -19.089	7.963	21.201
ATOM	599	CD2			63		-14.511	6.211	20.219
ATOM	600	N	ILE		64 64		-14.185	7.153	20.305
ATOM	601	H	ILE ILE		64		-13.862	5.178	20.972
MOTA	602	CA C	ILE		64		-13.529	5.744	22.325
ATOM	603 604	o	ILE		64		-13.396	6.959	22.602
ATOM ATOM	605	СВ	ILE		64		-12.618	4.716	20.231
MOTA	606	CG1			64		-11.925	3.573	20.949
MOTA	607	CG2			64		-11.690	5.865	19.950
ATOM	608	CD1	ILE	A	64		-10.905	2.888	20.062
ATOM	609	N	GLU		65		-13.396	4.815	23.294
ATOM	610	H	GLU		65		-13.443	3.844	23.059 24.670
ATOM	611	CA	GLU		.65		-13.186	5.174 4.360	25.165
ATOM	612	C	GLU		65		-12.024 -11.943	3.112	25.056
MOTA	613	0	GLU		65 65		-11.943	4.823	25.405
ATOM	614	CB	GLU GLU		65 65		-14.739	5.610	26.646
MOTA	615	CG	الربى	A	05	_			

FIG. 1 IK SUBSTITUTE SHEET (RULE 26)

PCT/US00/30863

			25	146			
ATOM ATOM ATOM ATOM ATOM ATOM ATOM ATOM	616 617 618 619 620 621 622 623 624 625 626 627 628	OE1 OE2 N H CA C O CB CG1 CG2 CD1 N	GLU A GLU A ILE A	65 65 66 66 66 66 66 66 67	-16.131 -17.090 -16.269 -10.971 -11.009 -9.762 -9.571 -9.422 -8.600 -8.838 -7.231 -8.951 -9.776 -9.989	5.353 5.785 4.708 5.008 6.002 4.317 4.586- 5.732 4.907 4.669 4.326 5.982 3.567 2.659	27.115 26.413 28.163 25.610 25.717 25.947 27.413 27.880 25.126 23.633 25.554 22.856 28.261 27.902
ATOM ATOM	629 63:0	H CA	CYS A	67 67	-9.698	3.740	29.687
ATOM ATOM ATOM	631 632 633	C O CB	CYS A CYS A	67 67 67	-10.673 -10.393 -8.251 -7.170	4.871 5.716 4.003 2.529	30.088 30.958 30.156 30.217
MOTA MOTA	634 635	SG N	CYS A GLY A	67 68	-11.877	4.947	29.499 28.791
MOTA MOTA	636 637	H CA	GLY A GLY A	68 68 68	-12.125 -12.788 -12.581	4.286 5.984 7.322	29.903 29.241
MOTA MOTA	638 639	С 0	GLY A	68	-13.404 -11.504	8.253 7.545	29.376 28.471
ATOM ATOM	640 641	N H	HIS A	69 69	-10.817	6.827	28.360 27.793
MOTA	642	CA C	HIS A	69 69	-11.305 -11.838	8.800 8.679	26.399
ATOM ATOM	643 644	, 0	HIS A	69	-11.516 -9.831	7.742 9.128	25.630 27.724
ATOM ATOM	645 646	CB CG	HIS A	69 69	-9.276	9.286	29.081
MOTA	647	ND1	HIS A	69	-9.317 -9.688	10.484 11.347	29.778 29.436
MOTA MOTA	648 649	HD1 CD2		69 69	-8.723	8.352	29.912
ATOM	650	CEl	HIS A	69	-8.783	10.254 8.990	30.947 31.091
MOTA	651	NE2		69 70	-8.405 -12.768	9.561	25.973
MOTA	652	N H	LYS A	70	-13.084	10.284	26.588
ATOM ATOM	653 654	CA	LYS A	70	-13.325	9.492	24.646
MOTA	655	C	LYS A	70	-12.346	10.074 11.055	23.653 23.864
MOTA	656	0	LYS A	70	-11.587 -14.645	10.285	24.536
ATOM	657	CB	LYS A	70 70	-15.837	9.703	25.330
MOTA	658 659	CG CD	LYS A LYS A	70	-17.105	10.593	25.286
ATOM ATOM	660	CE	LYS A	70	-18.293	10.011	26.092
ATOM	661	NZ	LYS A	70	-18.802	8.702	25.608 26.185
ATOM	662	1HZ	LYS A	70	-19.563	8.406 8.023	25.650
MOTA	663	3HZ	LYS A	70	-18.069 -19.116	8.795	24.663
MOTA	664	2HZ	LYS A	70 71	-12.323	9.485	22.446
MOTA	665	N H	ALA A ALA A		-12.813	8.625	22.305
MOTA	666 667		ALA A		-11.616	10.044	21.333
MOTA MOTA	668	C	ALA A		-12.529	9.795	20.171
ATOM	669		ALA A	71	-13.351	8.850	20.146 21.143
ATOM	670		ALA A		-10.292	9.358 10.685	19.149
ATOM	671	N	ILE A	72	-12.559	10.003	

FIG. I L SUBSTITUTE SHEET (RULE 26)

26/46

			TT D		72		-12.006	11.517	19.200
MOTA	672	H	ILE		72		-13.376	10.474	17.963
MOTA	673	CA		A	72			10.662	16.771
ATOM	674	С		A	72		-12.480		16.550
ATOM	675	0	ILE	Α	72		-11.858	11.720	17.882
ATOM	676	CB	ILE	Α	72		-14.541	11.464	
ATOM	677	CG1	ILE	Α	72		-15.306	11.455	19.196
ATOM	678	CG2		Α	72		-15.429	11.203	16.651
ATOM	679	CD1		Α	72		-16.446	12.415	19.176
ATOM	680	N	GLY		73		-12.252	9.633	15.958
	681	H	GLY		73		-12.778	8.789	16.067
ATOM		CA	GLY		73		-11.253	9.755	14.938
ATOM	682		GLY		73		-11.283	8.554	14.034
MOTA	683	C			73		-12.211	7.706	14.006
MOTA	684	0	GLY				-10.247	8.428	13.182
ATOM	685	N	THR		74		-9.471	9.055	13.250
MOTA	68.6	H	THR		74			7.416	12.158
ATOM	687	CA	THR		74		-10.201		12.760
ATOM	688	С		Α	74	•	-9.674	6.134	13.497
MOTA	689	0	THR	Α	74		-8.670	6.034	11.048
MOTA	690	CB .	THR	Α	74		-9.298	7.895	
MOTA	691	OG1	THR	Α	74		-9.910	9.019	10.441
ATOM	692	HG1	THR	Α	74		-9.335	9.362	9.698
ATOM	693	CG2	THR	Α	74		-9.088	6.823	9.946
ATOM	694	N	VAL	Α	75		-10.318	5.027	12.327
ATOM	695	H	VAL	Α	75		-11.066	5.114	11.669
ATOM	696	CA	VAL	Α	75		-9.968	3.717	12.778
ATOM	697	С	VAL		75	,	-9.906	2.843	11.551
ATOM	698	Ö	VAL		75		-10.803	2.807	10.681
ATOM	699	CB	VAL		75		-11.044	3.250	13.737
ATOM	700	CG1	VAL		75		-11.021	1.721	13.943
ATOM	701	CG2	VAL		75		-10.915	4.019	15.034
MOTA	702	N	LEU		76		-8.768	2.139	11.366
ATOM	703	Н	LEU		76		-8.002	2.260	11.998
ATOM	704	CA	LEU		76		-8.566	1.183	10.276
ATOM	705	C	LEU		76		-8.848	-0.211	10.808
	705	o	LEU		76		-8.514	-0.582	11.958
MOTA	707	CB	LEU		76		-7.103	1.270	9.798
MOTA	708	CG	LEU		76		-6.608	2.684	9.443
MOTA			LEU		76		-5.151	2.645	9.087
MOTA	709	CD1			76		-7.396	3.302	8.296
ATOM	710	CD2	LEU	_	77		-9.569	-1.062	10.042
ATOM	711	N	VAL				-9.894	-0.766	9.144
ATOM	712	H	VAL		77		-9.899	-2.428	10.485
MOTA	713	CA	VAL		77		-9.298	-3.412	9.482
MOTA	714	C	VAL		77		-9.450	-3.300	8.253
ATOM	715	0	VAL		77		-11.436	-2.592	10.506
MOTA	716	CB	VAL		77			-4.021	10.682
MOTA	717	CG1			77		-11.830	-1.765	11.634
ATOM	718	CG2			77		-12.072	-4.402	9.928
MOTA	719	N	GLY		78		-8.560		10.913
MOTA	720	H	GLY		78		-8.445	-4.530	8.987
MOTA	721	CA	GLY		78		-7.930	-5.285	9.732
ATOM	722	C	GLY		78		-7.228	-6.380	
ATOM	723	0	GLY		78		-7.292	-6.524	10.970
ATOM	724	N	PRO	A	79		-6.512	-7.271	9.003
ATOM	725	CA	PRO		79		-5.880	-8.467	9.602
ATOM	726	С	PRO	A	79		-4.599	-8.107	10.340
ATOM	727	0	PRO	Α	79		-3.449	-8.489	10.032

FIG. I IM

SUBSTITUTE SHEET (RULE 26)

	*	2	7/46	•		
	720	CB PRO A	79	-5.613	-9.379	8.400
ATOM	728 729	CG PRO A	79	-5.529	-8.416	7.210
MOTA	730	CD PRO A	79	-6.415	-7.225	7.537
MOTA	731	N THR A	80	-4.759	-7.304	11.408
MOTA	732	H THR A	80	-5.664	-6.935	11.619
ATOM	733	CA THR A	80	-3.658	-6.957	12.263
ATOM ATOM	734	C THR A	80	-3.490	-8.075	13.308
ATOM	735	O THR A	80	-4.447	-8.642	13.857
ATOM	736	CB THR A	80	-3.868	-5.572	12.927 13.787
ATOM	737	OG1 THR A	80	-2.770	-5.303	14.225
ATOM	738	HG1 THR A	80	-2.889	-4.412	13.678
ATOM	739	CG2 THR A	80	-5.210	-5.464 -8.496	13.589
ATOM	740	N PRO A		-2.243	-8.496 -9.476	14.660
ATOM	741	CA PRO A		-1.986	-9.476 -8.952	16.001
ATOM	742	C PRO A		-2.499	-8.932 -9.720	16.866
ATOM	743	O PRO A		-2.944	-9.720 -9.549	14.732
MOTA	744	CB PRO A		-0.444	-8.951	13.429
ATOM	745	CG PRO A		0.069	-8.105	12.842
ATOM	746	CD PRO A		-1.029	-7.621	16.276
MOTA	747	N VAL A		-2.474 -2.180	-6.975	15.571
ATOM	748	H VAL A		-2.180 -2.869	-7.091	17.591
MOTA	749	CA VAL A	_	-3.605	-5.761	17.379
MOTA	750	C VAL A		-3.349	-5.004	16.429
MOTA	751	O VAL A	_	-1.595	-6.858	18.443
ATOM	752	CB VAL A	_	-0.650	-5.824	17.803
MOTA	753	CG1 VAL A		-1.907	-6.418	19.890
MOTA	754	CG2 VAL A		-4.548	-5.371	18.260
MOTA	755	N ASN A		-4.810	-5.981	19.007
MOTA	756	H ASN A		-5.181	-4.067	18.123
MOTA	757	CA ASN A		-4.195	-3.019	18.565
MOTA	758			-3.605	-3.064	19.665
MOTA	759	O ASN A		-6.436	-3.942	18.982
ATOM	760 761	CG ASN A		-7.502	-4.930	18.631
MOTA	762	OD1 ASN A		-7.899	-5.049	17.488
MOTA	763	ND2 ASN A		-7.980	-5.662	19.628
ATOM ATOM	764	2HD2 ASN A		-8.695	-6.341	19.459
ATOM	765	1HD2 ASN A		-7.630	-5.541	20.557
MOTA	766	N ILE	A 84	-4.007	-1.951	17.770
ATOM	767			-4.583	-1.827	16.962
ATOM	768			-2.993	-0.954	18.032 18.114
ATOM	769		A 84	-3.679	0.387	17.240
ATOM	770			-4.460	0.797	16.833
ATOM	771			-2.021	-0.922	16.859
MOTA	772	CG1 ILE		-1.162	-2.150	16.747
ATOM	773	CG2 ILE		-1.219	0.387 -2.360	15.579
ATOM	774	CD1 ILE		-0.375	1.155	19.203
MOTA	775			-3.471	0.781	19.985
MOTA	776			-2.972 -3.951	2.518	19.281
MOTA	777			-2.784	3.425	18.949
ATOM	778			-1.767	3.515	19.663
ATOM	779		A 85	-4.522	2.825	20.676
MOTA	780	,	A 85	-5.673	1.865	21.050
ATOM	781			-5.000	4.274	20.716
ATOM	782			-6.828	1.808	20.059
MOTA	783	CD1 ILE	A 85	5.020		

FIG. IN SUBSTITUTE SHEET (RULE 26)

				28	3/46			
ATOM	784	N	GLY	Α	86	-2.820	4.123	17.792
ATOM	785	H	GLY		86	-3.637	4.087	17.217
ATOM	786	CA	GLY	Α	86	-1.690	4.936	17.351
ATOM	787	С	GLY		86	-1.831	6.393	17.704
ATOM	788	0	GLY	Α	86	-2.760	6.864	18.390
ATOM	789	N	ARG	Α	87	-0.881	7.229	17.230
ATOM	790	H	ARG	Α	87	-0.204	6.890-	16.577
ATOM	791	CA	ARG		87	-0.810	8.623	17.643
MOTA	792	С	ARG		87	-2.027	9.445	17.277
ATOM	793	0	ARG		87	-2.365	10.430	17.963 17.057
ATOM	794	CB	ARG		87	0.450	9.275	17.057
ATOM	795	CG	ARG		87	1.735	8.496	16.207
MOTA	796	CD	ARG		87	2.762	8.916 7.961	16.207
MOTA	797	NE	ARG		87	3.875	7.353	16.895
MOTA	79.8	HE	ARG		87	4.035	7.893	15.035
ATOM	799	CZ	ARG		87	4.660	8.675	13.975
ATOM	800	NH1	ARG		87	4.463 3.712	9.335	13.974
ATOM	801	2HH1	ARG		87	5.066	8.602	13.181
ATOM	802	1HH1	ARG		87	5.656	7.019	15.023
ATOM	803	NH2	ARG ARG		87 87	6.254	6.953	14.224
ATOM	804	1HH2	ARG		87	5.810	6.426	15.813
MOTA	805	2HH2 N	ASN		88	-2.780	9.120	16.214
ATOM	806 807	H	ASN		88	-2.504	8.361	15.625
ATOM	808	CA	ASN		88	-4.015	9.860	15.890
ATOM ATOM	809	C	ASN		88	-4.963	9.921	17.069
MOTA	810	Ö	ASN		88	-5.613	10.954	17.345
ATOM	811	CB	ASN		88	-4.712	9.315	14.617
ATOM	812	CG	ASN		88	-5.475	8.001	14.827
ATOM	813		ASN		88	-4.922	6.996	15.245
ATOM	814	ND2	ASN		88	-6.758	7.998	14.506
ATOM	815	2HD2	ASN	Α	88	-7.306	7.169	14.622
ATOM	816	1HD2	ASN	A	88	-7.190	8.824	14.145
MOTA	817	N	LEU	Α	89	-5.130	8.847	17.848
ATOM	818	H	LEU		89	-4.637	8.002	17.640
ATOM	819	CA	LEU		89	-6.024	8.865	19.013
MOTA	820	С	LEU	Α	89	-5.275	9.091	20.309
MOTA	821	0	LEU		89	-5.834	9.632	21.283 19.140
MOTA	822	CB	LEU		89	-6.840	7.592 7.355	17.957
MOTA	823	CG	LEU		89	-7.759	5.980	18.088
MOTA	824	CD1	LEU		89	-8.369	8.457	17.801
ATOM	825	CD2	LEU		89	-8.817 -3.983	8.745	20.428
ATOM	826	N	LEU		90	-3.525	8.274	19.674
ATOM	827	H	LEU		90 90	-3.242	9.057	21.664
MOTA	828	CA	LEU		90	-3.155	10.555	21.932
ATOM	829	C	LEU		90	-3.202	11.020	23.092
ATOM	830	O CB	LEU LEU		90	-1.817	8.453	21.661
ATOM	831 832	CG	LEU		90	-1.766	6.914	21.587
ATOM	833	CD1	LEU		90.	-0.343	6.494	21.396
ATOM ATOM	834	CD1	LEU		90	-2.339	6.230	22.812
ATOM	835	N CD2	THR		91	-3.031	11.407	20.926
MOTA	836	Н	THR		91	-2.982	11.063	19.988
ATOM	837	CA	THR		91	-2.964	12.834	21.155
ATOM	838	c.	THR		91	-4.309	13.331	21.635
ATOM	839		THR		91	-4.422	14.315	22.398

FIG. LIO SUBSTITUTE SHEET (RULE 26)

29/46 13.543 19.848 -2.555 91 THR A **ATOM** 840 CB 18.802 -3.459 13.214 91 THR A 841 OG1 MOTA 17.958 -3.188 13.677 HG1 THR A 91 842 MOTA 13.122 19.395 -1.153 91 CG2 THR A 843 ATOM 12.704 21.258 -5.435 92 GLN A 844 N MOTA 11.892 20.677 -5.379 92 GLN A 845 Η MOTA 13.186-21.682 -6.763 GLN A 92 846 CA **ATOM** 12.975 23.153 -6.942 GLN A 92 847 C ATOM -7.554 23.871 13.797 0 GIN A 92 848 MOTA 20.964 12.479 -7.890 GLN A 92 CB 849 MOTA 19.517 -7.937 12.862 GLN A 92 CG 850 **ATOM** 18.886 12.515 -9.251 GLN A 92 851 CD MOTA 19.546 12.424 -10.270OE1 GLN A 92 852 MOTA 17.588 12.323 92 -9.202 NE2 GLN A 853 MOTA 17.080 -10.031 12.087 854 1HE2 GLN A 92 MOTA 17.097 -8.336 12.411 2HE2 GLN A 92 855 MOTA 23.721 -6.472 11.846 93 ILE A 856 N MOTA 23.155 11.160 -6.014 93 ILE A 857 Н MOTA 11.578 25.165 -6.608 93 ILE A CA MOTA 858 12.189 25.948 -5.472 ILE A 93 C **MOTA** 859 27.171 12.031 -5.342 93 ILE Α 0 **ATOM** 860 25.484 10.073 -6.820 93 ILE Α 861 CB MOTA 25.286 -5.536 9.221 CG1 ILE 93 Α **ATOM** 862 9.486 24.735 93 -8.022 CG2 ILE A **ATOM** 863 7.740 25.693 -5.754 CD1 ILE A 93 864 MOTA 25.330 12.993 -4.594 GLY A 94 MOTA 865 N 24.334 13.079 -4.617 GLY A 94 **MOTA** 866 Н 26.063 13.742 -3.613GLY A 94 CA MOTA 867 26.512 -2.448 12.895 GLY A 94 C MOTA 868 27.519 -1.76413.158 94 GLY A MOTA 869 0 25.797 -2.117 11.849 95 CYS A MOTA 870 N 24.957 -2.619 11.644 95 CYS A **ATOM** 871 Н -1.036 10.994 26.214 CYS A 95 872 CA MOTA 25.925 0.362 11.566 95 CYS A 873 C ATOM 24.907 0.588 12.254 95 CYS A 874 0 **ATOM** -1.260 9.655 25.550 CYS A 95 875 CB **ATOM** 26.125 8.307 CYS A -0.254 95 SG **ATOM** 876 26.803 11.297 1.346 96 THR A 877 N MOTA 27.618 10.738 1.135 96 878 H THR A MOTA 11.779 26.664 2.728 96 879 CA THR A **ATOM** 10.784 27.264 3.729 96 880 C THR A MOTA 28.345 10.249 3.498 96 881 O THR A MOTA 13.154 27.346 2.925 882 CB THR A 96 MOTA 2.594 13.109 28.721 OG1 THR A 96 MOTA 883 13.966 29.109 2.784 HG1 THR A 96 884 **ATOM** 14.300 26.698 2.139 CG2 THR A 96 885 MOTA 10.603 26.599 4.882 97 N LEU A 886 MOTA 11.071 25.714 5.016 LEU A 97 MOTA 887 Н 27.166 9.910 6.040 97 CA LEU A MOTA 888 28.175 6.751 10.824 97 C LEU A 889 MOTA 28.044 6.705 12.046 LEU A 97 0 ATOM 890 26.049 9.497 7.013 LEU A 97 CB MOTA 891 25.065 8.449 6.452 LEU A 97 892 CG **ATOM** 8.355 23.828 7.360 CD1 LEU A 97 **ATOM** 893 25.724 7.065 97 6.345 CD2 LEU A MOTA 894 29.175 7.412 10.221 ASN A 98 N MOTA 895

FIG. 1P SUBSTITUTE SHEET (RULE 26)

			3	0/46	•		
ATOM ATOM ATOM ATOM ATOM ATOM ATOM ATOM		CA I C C I C C C C C C C C C C C C C C C	ASN A A A A A A A A A A LEU A LEU A LEU A LEU A LEU A	0/46 9888888999999999999999999999999999999	7.413 8.065 9.220 8.995 7.057 6.084 4.983 6.493 5.888 7.406 10.451 10.547 11.679 12.711 12.487 12.233 12.833 11.876	9.212 10.897 10.029 9.079 11.177 12.305 12.062 13.549 14.331 13.707 10.369 11.177 9.620 10.437 11.652 8.989 9.873 10.947 10.505 9.819	29.205 30.292 30.800 31.550 31.423 31.083 30.594 31.342 31.136 31.742 30.389 29.792 30.666 31.454 31.651 29.369 28.248 27.705 28.623 31.869
TER ATOM ATOM ATOM ATOM ATOM ATOM ATOM ATOM	916 917 918 919 920 921 922 923 924 925 926	N CA C O CB CG CD 1H 2H N	PRO B PRO B PRO B PRO B PRO B PRO B PRO B PRO B PRO B PRO B	1 1 1 1 1 1 1 1 2	12.600 11.842 10.430 10.054 12.622 13.817 13.966 12.175 12.594 9.513 9.751	14.237 15.268 14.773 13.695 15.412 14.470 14.227 13.343 14.457 15.542 16.474	30.106 29.363 29.138 29.618 28.035 28.131 29.603 29.964 31.081 28.523 28.251
ATOM ATOM ATOM ATOM ATOM ATOM ATOM ATOM	927 928 929 930 931 932 933 934 935	CA C O CB CC CD OE1 NE2 1HE2 2HE2	GLN B	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	8.186 8.066 8.523 7.155 5.739 4.744 4.628 4.024 3.341 4.160	15.058 15.151 16.140 15.976 15.732 16.365 15.962 17.367 17.830 17.665	28.242 26.749 26.133 28.856 28.373 29.284 30.431 28.784 29.349 27.839 26.036
ATOM ATOM ATOM ATOM ATOM ATOM ATOM ATOM	937 938 939 940 941 942 943 944 945 946	N H CA C O CB CG1 CG2 CD1	ILE E	3 3 3 3 3 3 3 3 3 3 3 3 4	7.499 7.102 7.435 5.956 5.150 8.299 9.743 8.269 10.621 5.462 6.046	14.176 13.386 14.216 14.097 13.290 13.058 13.232 12.985 12.068 15.108 15.887	26.504 24.601 24.184 24.710 24.029 24.534 22.496 24.143 23.453 23.226
ATOM ATOM ATOM ATOM	947 948 949 950	CA C	THR I	3 4 3 4	4.107 4.039 5.066	15.115 14.193 13.755	22.976 21.765 21.203

FIG. I IQ SUBSTITUTE SHEET (RULE 26)

WO 01/35316 PCT/US00/30863 ·

31/46										
ATOM	951	CB	THR	В	4	3.616	16.548	22.647		
MOTA	952	OG1	THR	В	4	4.450	17.157	21.645		
ATOM	953	HG1	THR	В	4	4.123	18.080	21.442		
ATOM	954	CG2	THR	В	4	3.644	17.454	23.876		
ATOM	955	N	LEU	В	5	2.872	13.781	21.324		
ATOM	956	H	LEU	В	5	2.033	14.151	21.723		
ATOM	957	CA		В	5	2.837	12.795~			
ATOM	958	С	LEU	В	5	2.183	13.415	19.047		
ATOM	959	0	LEU	В	5	1.677	12.720	18.14.2		
ATOM	960	CB	LEU	В	5	2.093	11.577	20.762		
ATOM	961	CG	LEU	В	5	2.819	10.856	21.892		
ATOM	962	CD1	LEU	В	5	1.889	9.885	22.602		
MOTA	963	CD2	LEU	В	, 5	4.108	10.159	21.416		
ATOM	964	N	TRP	В	6	2.209	14.742	18.880 19.593		
ATOM	965	H	TRP	В	6	2.601	15.323 15.364	17.690		
ATOM	966	CA	TRP	В	. 6	1.683	14.978	16.509		
MOTA	967	C	TRP	В	. 6	2.581 2.159	14.978	15.349		
ATOM	968	0	TRP	В	6 6	1.587	16.879	17.833		
MOTA	969	CB	TRP TRP	B	6	0.652	17.339	18.921		
ATOM	970	CG	TRP	B B	6	0.955	17.584	20.232		
MOTA	971 972	CD1 CD2	TRP	В	6	-0.750	17.612	18.783		
ATOM	973	NE1	TRP	В	6	-0.167	17.989	20.913		
MOTA MOTA	974	HE1	TRP	В	6	-0.217	18.230	21.882		
ATOM	975	CE2	TRP	В	6	-1.224	18.013	20.048		
ATOM	976	CE3	TRP	В	6	-1.637	17.550	17.709		
ATOM	977	CZ2	TRP	В	6	-2.544	18.352	20.266		
MOTA	978	CZ3	TRP	В	6	-2.947	17.885	17.921		
ATOM	979	CH2	TRP	В	6	-3.394	18.281	19.185		
ATOM	980	N	GLN	В	7	3.896	14.809	16.738		
ATOM	981	H	GLN	В	7	4.267	14.985	17.650		
ATOM	982	CA	GLN	В	7	4.794	14.376	15.689		
ATOM	983	C	GLN	В	7	5.361	13.043	16.096		
MOTA	984	0		В	7	5.221	12.586	17.243		
MOTA	985	CB		В	7	5.880	15.430	15.505		
ATOM	986	CG	GLN	B	7	5.353	16.704	14.804 15.137		
MOTA	987	CD		B	7	6.197	17.912 17.802	15.404		
ATOM	988	OE1	GLN	_	7	7.400 5.553	19.083	15.121		
ATOM	989	NE2	GLN		7 7	6.040	19.003	15.330		
ATOM	990	1HE2		B B	7	4.579	19.121	14.900		
ATOM	991 992	2HE2 N		В	8	5.979	12.274	15.189		
ATOM ATOM	993	H	AŖG		8	6.073	12.597	14.247		
ATOM	994	CA	ARG		8	6.505	10.985	15.573		
MOTA	995	C.		В	8	7.577	11.198	16.610		
ATOM	996	Ö		В	8	8.395	12.130	16.515		
ATOM	997	CB	ARG		. 8	7.092	10.238	14.384		
ATOM	998	CG	ARG		8	6.132	10.018	13.237		
ATOM	999	CD		В	8	6.802	9.4.02	12.046		
MOTA	1000	NE	ARG	В	8	5.846	9.005	11.023		
MOTA	1001	HE		В	8	4.872	9.080	11.237		
MOTA	1002	CZ	ARG		8	6.217	8.552	9.828		
MOTA	1003	NHl		В	8	7.496	8.442	9.486		
MOTA	1004	2HH1	,	В	8	8.211	8.703	10.134		
ATOM	1005	1HH1		В	8	7.744	8.098	8.580		
ATOM	1006	NH2	ARG	В	8	5.279	8.202	8.952		

FIG. I IR SUBSTITUTE SHEET (RULE 26)

				32	2/46			·
» mon	1007	1HH2	ARG	в	8	5.540	7.860	8.050
ATOM		2HH2		B.	8	4.312	8.281	9.196
MOTA	1008	N		В	9	7.663	10.381	17.682
ATOM	1010	CA		B	9		10.587	18.746
MOTA	1011	C		В	9	10.065	10.196	18.315
MOTA	1011	0	PRO	В	9	10.678	9.215	18.778
ATOM	1012	CB		В	9	8.148	9.682	19.878
ATOM ATOM	1013	CG		В	9	7.315	8.607	19.206
ATOM	1015	CD	PRO	В	9	6.708	9.323	18.004
ATOM	1016	N	LEU	В	10		10.969	17.400
ATOM	1017	Н	LEU		10		11.746	16.998
ATOM	1018	CA	LEU	В	10		10.706	16.978
ATOM	1019	С		В	10		11.498	17.850 18.018
ATOM	1020	0	LEU	В	10		12.733	15.554
MOTA	1021	CB	LEU	В	10		11.170	14.551
ATOM	1022	CG	LEU	В	10		10.386	13.276
ATOM	1023	CD1		В	10		11.175	14.355
MOTA	1024	CD2		В	10	11.956	8.947 10.843	18.384
MOTA	1025	N		В	11		9.866	18.206
ATOM	1026	H	VAL	В	11	14.148 15.018	11.517	19.223
ATOM	1027	CA		В	11	16.400	11.111	18.740
MOTA	1028	C		В	11	16.581	10.201	17.911
MOTA	1029	0_	VAL		11	14.857	11.100	20.699
MOTA	1030	CB	VAL	В	11 11	13.514	11.586	21.293
ATOM	1031	CG1	VAL	B B	11	15.038	9.573	20.903
MOTA	1032	CG2	THR		12	17.485	11.739	19.232
MOTA	1033	N	THR		12	17.370	12.507	19.862
ATOM	1034	H CA	THR		12	18.843	11.325	18.868
MOTA	1035 1036	C	THR	В	12	19.377	10.284	19.837
MOTA	1036	Ö	THR	В	12	19.237	10.352	21.082
ATOM ATOM	1037	CB	THR	В	12	19.830	12.520	18.820
ATOM	1038	OG1	THR	В	12	19.389	13.483	17.876
ATOM	1040	HG1	THR	В	12	20.028	14.252	17.848
ATOM	1041	CG2	THR	В	12	21.234	12.075	18.399
ATOM	1042	N	ILE	В	13	20.044	9.234	19.338
ATOM	1043	H	ILE	В	13	20.135	9.130	18.348 20.176
ATOM	1044	CA	ILE	В	13	20.641	8.239	19.855
ATOM	1045	С	ILE		13	22.119	8.226	18.865
MOTA	1046	0	ILE		13	22.579	8.817 6.870	19.879
MOTA	1047	CB	ILE		13	19.993	6.464	18.415
MOTA	1048	CG1			13	20.192	6.893	20.206
MOTA	1049	CG2			13	18.482 19.829	5.035	18.106
ATOM	1050	CD1			13	22.973	7.618	20.661
MOTA	1051	N	LYS		14	22.652	7.243	21.531
ATOM	1052	H	LYS		14 14	24.364	7.480	20.317
MOTA	1053	CA	LYS		14	24.680	6.029	20.477
ATOM	1054	C O	LYS LYS		14	24.353	5.353	21.484
MOTA	1055	CB	LYS		14	25.266	8.263	21.242
MOTA	1056	CG	LYS		14	24.947	9.729	21.236
MOTA	1057 1058	CD	LYS		14	25.664	10.498	22.339
ATOM ATOM	1058	CE	LYS		14	26.758	11.441	21.807
ATOM	1059	NZ	LYS		14	28.026	10.781	21.440
ATOM	1061	1HZ	LYS		14	28.674	11.466	21.107
MOTA	1062	3HZ	LYS		14	27.855	10.107	20.722

FIG. 1 IS

33/46 22.243 10.323 14 28.408 2HZ LYS B 1063 MOTA 19.425 5.390 25.214 15 ILE B 1064 N MOTA 18.594 5.901 25.434 ILE B 15 1065 Η MOTA 3.989 19.434 25.489 15 ILE B 1066 CA MOTA 18.750 3.981 26.832 15 ILE B C 1067 MOTA 17.933 4.869 27.104 ILE B 15 1068 0 MOTA 3.220 18.606 24.435 ILE B 15 1069 CB MOTA 18.347 1.824 24.893 CG1 ILE B 15 MOTA 1070 17.309 24.048 3.977 15 CG2 ILE B MOTA 1071 0.996 23.830 17.645 CD1 ILE В 15 1072 ATOM 19.202 3.212 27.812 GLY В 16 1073 N MOTA 19.913 2.535 27.623 GLY B 16 1074 Н **ATOM** 29.175 3.336 18.677 GLY B 16 1075 CA **ATOM** 29.771 4.754 18.619 16 1076 C GLY B ATOM 17.902 4.970 30.737 16 1077 GLY B 0 MOTA 19.335 5.791 29.273 GLY B 17 1078 N MOTA 5.660 19.892 28.453 GLY B 17 1079 Η ATOM 7.105 19.302 29.924 GLY B 17 CA MOTA 1080 18.176 8.043 29.468 GLY B 17 C MOTA 1081 17.933 9.155 29.984 17 GLY B 0 1082 MOTA 7.621 17.411 28.433 GLN B 18 MOTA 1083 N 17.560 6.711 28.046 GLN B 18 MOTA 1084 Η 16.348 8.449 27.834 18 GLN B CA MOTA 1085 16.736 8.755 26.407 GLN B 18 **ATOM** 1086 C 17.353 7.953 25.678 GLN B 18 **ATOM** 1087 0 15.045 7.645 27.810 GLN B 18 MOTA 1088 CB 15.146 27.247 6.204 18 GLN B ··· ATOM 1089 CG 5.333 13.924 27.572 GLN B 18 CD MOTA 1090 4.501 13.464 26.771 OE1 GLN B 18 MOTA 1091 13.393 5.531 28.766 NE2 GLN B 18 MOTA 1092 12.594 5.005 29.057 1093 1HE2 GLN B 18 ATOM 13.786 29.388 6.209 2HE2 GLN B 18 MOTA 1094 16.337 9.933 25.873 LEU B 19 MOTA 1095 N 15.863 10.602 26.446 LEU B 19 1096 Н MOTA 16.578 10.267 24.467 LEU B 19 CA 1097 ATOM 15.490 9.622 23.633 19 LEU B C ATOM 1098 14.284 9.707 23.912 19 LEU B MOTA 1099 0 16.457 11.777 24.207 19 LEU B CB 1100 MOTA 17.454 24.857 12.756 LEU B 19 CG MOTA 1101 18.880 12.335 24.739 CD1 LEU B 19 1102 ATOM 13.072 17.130 26.299 19 CD2 LEU B 1103 MOTA 15.850 22.450 9.085 20 LYS B N MOTA 1104 16.819 22.242 8.948 20 LYS B MOTA 1105 Н 14.867 8.702 21.472 20 LYS B CA MOTA 1106 15.417 9.105 20.121 LYS B 20 1107 C MOTA 16.569 19.957 9.572 LYS B 20 1108 0 ATOM 14.560 7.200 21.496 LYS B 20 MOTA 1109 CB 14.507 6.653 22.904 LYS B 20 MOTA 1110 CG 13.677 23.052 5.366 20 1111 CD LYS B MOTA 12.145 23.069 5.603 LYS B 20 CE MOTA 1112 11.699 6.758 23.893 LYS B 20 MOTA 1113 NZ 10.703 6.836 23.847 20 LYS B 1114 1HZ **ATOM** 11.978 6.617 24.843 LYS B 20 1115 3HZ **ATOM** 12.116 23.544 7.597 20 LYS B 1116 2HZ **ATOM** 14.591 9.022 19.068 GLU B 21 N MOTA 1117 13.650 8.712 19.200 GLU B 21 1118 Н MOTA

FIG. 11T SUBSTITUTE SHEET (RULE 26)

				34/	46			
ATOM	1119	CA	GLU I	В 2	1	17.735	9.366	15.008
ATOM	1120	C		B 2		16.937	8.095	15.119
ATOM	1121	0	GLU I		1	17.117	7.103	14.376
ATOM	1122	CB	GLU I	3 2	1	17.143	10.314	13.983
ATOM	1123	CG	GLU I	3 2	1	15.714	10.706	14.162
ATOM	1124	CD	GLU I	3 2	1	15.304	11.607	13.036
ATOM	1125	OE1	GLU I	3 2	1	14.971	11.051	11.957
MOTA	1126	OE2				15.338	12.854	13.174
MOTA	1127	N	ALA I			16.025	7.999	16.072
MOTA	1128	H	ALA I			15.825	8.792	16.648
ATOM	1129	CA	ALA I			15.300	6.783	16.315
MOTA	1130	C	ALA I			13.981	7.132 8.153	16.952 17.632
ATOM	1131	0	ALA I			13.756 16.095	5.865	17.032
ATOM	1132	CB	ALA E			12.994	6.230	16.743
MOTA	1133	N H	LEU E			13.195	5.379	16.257
ATOM ATOM	1134 1135	CA	LEU E			11.639	6.408	17.180
ATOM	1136	C	LEU E			11.476	5.740	18.534
ATOM	1137	Ö	LEU E			11.814	4.564	18.746
ATOM	1138	CB	LEU E			10.775	5.665	16.192
ATOM	1139	CG	LEU E			9.267	5.810	16.237
ATOM	1140	CD1	LEU E			8.807	7.142	15.664
ATOM	1141	CD2	LEU E	3 2:	3	8.648	4.625	15.482
ATOM	1142	N	LEU E	3 24	1	10.948	6.455	19.553
ATOM	1143	H	LEU E			10.775	7.433	19.435
ATOM	1144	CA	LEU E			10.613	5.838	20.849
ATOM	1145	С	LEU E			9.271	5.160	20.687
ATOM	1146	0	LEU E			8.208	5.764	20.418
MOTA	1147	CB	LEU E			10.564	6.878	21.971 22.075
MOTA	1148	CG	LEU E			11.828 11.580	7.750 8.859	23.077
ATOM	1149	CD1	LEU E			13.099	6.955	22.388
ATOM ATOM	1150 1151	CD2 N	LEU E			9.246	3.822	20.809
ATOM	1152	H	ASP E			10.025	3.347	21.218
ATOM	1153	CA	ASP E			8.122	3.030	20.366
ATOM	1154	C	ASP E			7.637	2.136	21.484
ATOM	1155	Ö	ASP E			8.189	1.048	21.759
ATOM	1156	CB	ASP E	3 25	5	8.613	2.196	19.189
ATOM	1157	CG	ASP E	3 25	5	7.528	1.421	18.511
ATOM	1158	OD1	ASP E			6.422	1.339	19.058
MOTA	1159	OD2				7.800	0.897	17.426
ATOM	1160	N	THR E			6.547	2.465	22.157
ATOM	1161	H	THR E			6.067	3.314	21.938 23.212
MOTA	1162	CA	THR E			6.025	1.621 0.369	22.694
ATOM	1163	C	THR E			5.347 4.976	-0.550	23.451
ATOM	1164	O	THR E			5.027	2.389	24.046
ATOM ATOM	1165 1166	CB OG1	THR E			3.927	2.853	23.239
ATOM	1167	HG1	THR E			3.277	3.359	23.806
ATOM	1168	CG2	THR E			5.703	3.603	24.650
ATOM	1169	N	GLY B			5.090	0.245	21.382
ATOM	1170	H	GLY B			5.341	0.983	20.756
ATOM	1171	CA	GLY B			4.457	-0.938	20.867
ATOM	1172	С	GLY B			5.475	-1.992	20.458
ATOM	1173	0	GLY B			5.121	-3.108	20.055
MOTA	1174	N	ALA B	28	3	6.792	-1.717	20.495

FIG. I IU

				35	146			
ATOM	1175	Н	ALA	В	28	7.104	-0.832	20.841
ATOM	1176		ALA		28	7.800	-2.690	20.037
ATOM	1177		ALA		28	8.371	-3.444	21.259
MOTA	1178	_	ALA		28	8.840	-2.807	22.213
ATOM	1179			В	28	8.924	-1.936	19.358
ATOM	1180			В	29	8.459	-4.787	21.289
ATOM	1181			B	29	8.082	-5.325	20.535
ATOM	1182		ASP	В	29	9.121	-5.441	22.452
ATOM	1183		ASP	В	29	10.608	-5.219	22.404
ATOM	1184	0	ASP	В	29	11.345	-5.264	23.412
ATOM	1185	CB	ASP	В	29.	8.965	-6.975	22.447
MOTA	1186		ASP	В	29	7.551	-7.477	22.774
MOTA	1187		ASP	В	29	6.683	-6.693	23.169
ATOM	1188		ASP	В	29	7.350	-8.686	22.616 21.171
ATOM	1189		ASP		30	11.164	-5.157	20.367
MOTA	1190		ASP		30	10.577	-5.063	20.387
ATOM	1191			В	30	12.609	-5.217	20.335
ATOM	1192		ASP	В	30	13.048	-3.886	19.817
MOTA	1193		ASP	В	30	12.269	-3.055 -6.226	19.735
ATOM	1194 .		ASP	В	30	12.833	-6.226 -7.675	20.099
MOTA	1195		ASP		30	12.477 13.197	-8.272	20.908
MOTA	1196		ASP	В	30	13.197	-8.272	19.569
MOTA	1197		ASP		30	14.387	-3.692	20.227
ATOM	1198	N	THR		31	15.018	-4.380	20.586
MOTA	1199	Н	THR		31	14.981	-2.530	19.614
MOTA	1200	CA	THR		31	15.578	-2.979	18.260
MOTA	1201	C	THR		31 31	16.246	-4.020	18.123
MOTA	1202	O	THR		31	16.036	-2.004	20.557
MOTA	1203	CB	THR THR	В	31	15.378	-1.376	21.645
MOTA	1204	OG1 HG1	THR		31	16.052	-1.016	22.290
ATOM	1205	CG2	THR		31	16.944	-0.960	19.904
ATOM	1206 1207	N	VAL		32	15.237	-2.283	17.150
MOTA MOTA	1207	H	VAL		32	14.703	-1.442	17.237
ATOM	1208	CA	VAL		32	15.626	-2.722	15.806
MOTA	1210	C	VAL		32	16.303	-1.566	15.132
ATOM	1211	ō	VAL		32	15.779	-0.428	14.995
ATOM	1212	CB	VAL		32	14.407	-3.126	14.964
ATOM	1213		VAL		32	14.820	-3.703	13.596
ATOM	1214	CG2	VAL		32	13.556	-4.102	15.703
ATOM	1215	N	LEU	В	33	17.563	-1.756	14.720
MOTA	1216	H	LEU	В	33	17.984	-2.658	14.814
MOTA	1217	CA	LEU	В	33	18.347	-0.697	14.138
MOTA	1218	С	LÉU		33	18.610	-1.009	12.685 12.205
MOTA	1219	۰0	LEU		33	18.685	-2.162	14.856
MOTA	1220	CB	LEU		33	19.679	-0.628	16.031
MOTA	1221	CG	LEU		33	19.698	0.363	16.891
MOTA	1222	CD1	LEU		33	18.425	0.321	16.889
MOTA	1223	CD2	LEU		33	20.929	0.179	11.899
MOTA	1224	N	GLU		34	18.786	0.078 0.991	12.271
MOTA	1225	H	GLU		34	18.619 19.218	0.041	10.488
MOTA	1226	CA	GLU		34	20.478	-0.774	10.399
MOTA	1227	C	GLU		34	21.374	-0.835	11.272
ATOM	1228	O	GLU		34 34	19.536	1.460	9.996
ATOM	1229	CB	GLU		34 34	20.722	2.088	10.761
MOTA	1230	CG	GLU	ם	24	20.722		•

FIG. 1 IV

PCT/US00/30863 WO 01/35316

36/46							
ATOM	1231	CD	GLU B	34	21.085	3.512	10.314
ATOM	1232	OE1	GLU B	34	20.285	4.466	10.500
	1233	OE2	GLU B	34	22.211	3.703	9.775
ATOM	1234	N	GLU B	35	20.673	-1.367	9.205
ATOM ATOM	1235	H	GLU B	35	20.011	-1.227	8.468
	1236	CA	GLU B	35	21.802	-2.205	8.930
ATOM ATOM	1237	C	GLU B	35	23.096	-1.520-	9.321
ATOM	1237	Ö	GLU B	35	23.391	-0.379	8.916
ATOM	1239	СВ	GLU B	35	21.741	-2.479	7.439
ATOM	1240	CG	GLU B	35	22.795	-3.380	6.883
MOTA	1241	CD	GLU B	35	22.987	-4.587	7.744
ATOM	1242	OE1	GLU B	35	21.980	-5.258	8.118 8.048
MOTA	1243	OE2	GLU B	35	24.149	-4.860	10.157
ATOM	1244	N	MET B	36	23.926	-2.106	10.137
ATOM	1245	H	MET B	36	23.654	-2.953	10.613
ATOM	1246	CA	MET B	36	25.232	-1.559	10.441
ATOM	1247	С	MET B	36	26.146	-2.687 -3.783	11.257
ATOM	1248	0	MET B	36	25.731	-0.424	11.497
MOTA	1249	CB	MET B	36	25.251	-0.424	12.881
ATOM	1250	CG	MET B	36	24.626	0.719	13.988
ATOM	1251	SD.	MET B	36	24.722 23.132	1.586	13.692
MOTA	1252	CE	MET B	36	27.441	-2.551	10.593
MOTA	1253	N	SER B	37	27.783	-1.726	10.144
MOTA	1254	H	SER B	37 37	28.321	-3.608	11.011
MOTA	1255	CA	SER B	37 37	28.721	-3.352	12.442
ATOM	1256	C	SER B	3 <i>1</i> 37	29.402	-2.369	12.788
ATOM	1257	O	SER B SER B	3 <i>7</i>	29.567	-3.622	10.109
ATOM	1258	CB	SER B	37	29.231	-3.908	8.750
MOTA	1259	OG HG	SER B	37	30.057	-3.911	8.187
MOTA	1260 1261	N	LEU B	38	28.469	-4.295	13.366
ATOM ATOM	1262	Н	LEU B	38	27.948	-5.123	13.117
ATOM	1263	CA	LEU B	38	29.073	-4.232	14.714
ATOM	1264	C	LEU B	38	30.132	-5.342	14.895
MOTA	1265	0	LEU B	38	30.070	-6.357	14.197
ATOM	1266	CB	LEU B	38	27.986	-4.237	15.802 15.750
ATOM	1267	CG	LEU B	38	27.005	-3.039	16.788
ATOM	1268	CD1		38	25.885	-3.214	16.700
MOTA	1269	CD2		38	27.707	-1.696 -5.160	15.804
ATOM	1270	N	PRO B	39	31.119	-6.116	16.052
ATOM	1271	CA	PRO B	39	32.199 31.767	-7.223	17.028
MOTA	1272	C	PRO B	39	31.767	-6.942	18.185
MOTA	1273	0_	PRO B	39	33.347	-5.276	16.625
ATOM	1274	CB	PRO B	39 39	32.634	-4.148	
MOTA	1275	CG	PRO B	39	31.385	-3.916	16.523
MOTA	1276	CD	PRO B GLY B	40	31.770	-8.481	16.559
ATOM	1277	N H	GLY B	40	32.036	-8.641	15.598
ATOM	1278	CA	GLY B	40	31.420	-9.658	17.353
ATOM	1279 1280	CA	GLY B	40	30.679	-10.723	16.539
ATOM	1280	o	GLY B	40	30.647	-10.671	15.308
MOTA MOTA	1282	N	LYS B	41	30.098	-11.699	17.255
MOTA	1283	Н	LYS B	41		-11.656	18.261
ATOM	1284	CA	LYS B	41		-12.861	16.702
ATOM	1285	C	LYS B	41	27.971	-12.923	17.245
ATOM	1286	0	LYS B	41	27.743	-12.700	18.436

FIG. I IW SUBSTITUTE SHEET (RULE 26)

37/46 30.154 -14.152 17.048 41 LYS B CB 1287 MOTA 16.384 31.537 -14.221 41 LYS B CG 1288 16.651 MOTA 32.192 -15.580 41 LYS B CD 1289 15.983 MOTA 33.566 -15.642 41 LYS B CE 1290 **ATOM** 34.198 -16.956 16.183 LYS B 41 NZ 1291 ATOM 35.102 -16.968 15.732 41 LYS B 1292 1HZ **ATOM** 33.612 -17.674 15.782 41 LYS B 3HZ 1293 ATOM 34.312 -17.128 17.172 41 2HZ LYS B 1294 27.018 -13.228 MOTA 16.351 42 TRP B N 1295 ATOM 15.411 27.307 -13.458 42 TRP B 1296 Н ATOM 16.521 25.597 -12.929 42 TRP B CA 1297 MOTA 24.723 -14.179 16.405 42 TRP B 1298 C MOTA 16.131 25.210 -15.277 42 TRP B 1299 0 ATOM 25.192 -11.856 15.491 42 TRP B CB 1300 ATOM 15.390 26.127 -10.687 42 TRP B CG ATOM 1301 14.244 26.651 -10.197 CD1 TRP B 42 1302 MOTA 16.467 -9.913 26.739 CD2 TRP B 42 1303 MOTA 14.533 -9.191 27.548 NE1 TRP B 42 MOTA 1304 13.818 -8.702 28.067 HE1 TRP B 42 1305 MOTA 15.893 -8.995 27.664 CE2 TRP B 42 1306 17.875 MOTA -9.923 26.640 CE3 TRP B 4.2 1307 MOTA 16.680 -8.136 28.443 42 CZ2 TRP B 1308 MOTA 18.673 -9.075 27.426 42 CZ3 TRP B 1309 MOTA 18.077 28.318 -8.171 CH2 TRP B 42 MOTA 1310 16.617 23.416 -13.980 LYS B 43 N MOTA 1311 23.105 -13.044 16.840 LYS B 43 1312 Н MOTA 16.526 22.378 -14.995 43 LYS B CA 1313 MOTA 15.478 21.368 -14.507 43 LYS B C 1314 MOTA 15.706 20.743 -13.472 43 LYS B 0 1315 MOTA 17.893 21.694 -15.196 43 LYS B CB 1316 MOTA 19.034 22.641 -15.623 LYS B 43 CG 1317 MOTA 20.323 22.409 -14.814 43 LYS B CD 1318 MOTA 20.182 22.767 -13.327 LYS B 43 CE 1319 MOTA 20.015 24.214 -13.113 LYS B 43 NZ 1320 MOTA 19.924 24.400 -12.125 43 LYS B 1321 1HZ MOTA 19.185 24.532 -13.593 LYS B 43 3HZ 1322 MOTA 20.821 24.702 -13.476 LYS B 43 2HZ 1323 MOTA 14.341 21.175 -15.204 44 PRO B 1324 N MOTA 13.382 20.139 -14.835 44 PRO B CA 1325 **ATOM** 14.044 18.765 -14.997 PRO B 44 C 1326 MOTA 14.860 18.573 -15.902 44 PRO B 1327 0 12.180 MOTA 20.341 -15.761 44 PRO B 1328 CB MOTA 20.999 -16.999 12.787 44 PRO B CG 1329 MOTA 13.933 21.837 -16.434 44 PRO B MOTA 1330 CD 13.712 17.825 -14.101 45 LYS B 1331 N MOTA 12.944 17.994 -13.483 45 LYS B 1332 H MOTA 14.339 16.523 -14.088 45 LYS B 1333 CA MOTA 13.329 15.519 -13.590 LYS B 45 1334 C **ATOM** 12.379 15.829 -12.838 LYS B 45 1335 0 MOTA 15.560 16.558 -13.149 LYS B 45 1336 CB MOTA 16.579 15.469 -13.442 LYS B 45 1337 CG MOTA 17.501 15.256 -12.254 45 LYS B 1338 CD ATOM 18.469 14.131 -12.461 LYS B 45 1339 CE MOTA 14.549 -13.442 19.474 45 LYS B 1340 NZ ATOM 20.126 13.805 -13.588 LYS B 45 ATOM 1341 1HZ 19.958 15.355 -13.101 LYS B 1342 3HZ MOTA

FIG. IX
SUBSTITUTE SHEET (RULE 26)

			38	146	
ATOM	1343 2	2HZ	LYS B	45	14.772 -14.306 19.023
ATOM	1344		MET B	46	14.240 -14.005 13.416
ATOM	1345		MET B	46	13.991 -14.705 14.085
ATOM	1346		MET B	46	13.203 -13.472 12.570
	1347		MET B	46	12.291 -12.623 13.425
MOTA	1347	_	MET B	46	11.782 -13.063 14.471
MOTA	1349	_	MET B	46	12.383 -14.616- 12.016
MOTA MOTA	1350	CG	MET B	46	13.153 -15.586 11.187
ATOM	1351	SD	MET B	46	12.977 -15.188 9.473
ATOM	1352	CE	MET B	46	13.566 -16.690 8.775
ATOM	1353	N	ILE B	47	11.933 -11.379 13.030
ATOM	1354	H	ILE B	47	12.327 -10.991 12.196
ATOM	1355	CA	ILE B	47	10.971 -10.568 13.797
ATOM	1356	C	ILE B	47	9.761 -10.233 12.962
ATOM	1357	Ö	ILE B	47	9.819 -10.048 11.731
ATOM	1358	CB	ILE B	47	11.608 -9.294 14.385
ATOM	1359	CG1	ILE B	47	12.345 -8.459 13.318
ATOM	1360	CG2	ILE B	47.	12.542 -9.638 15.494
ATOM	1361	CD1	ILE B	47	12.789 -7.123 13.851
ATOM	1362	N	GLY B	48	8.557 -10.136 13.558
ATOM	1363	Н	GLY B	48	8.484 -10.249 14.549
ATOM	1364	CA	GLY B	48	7.365 -9.872 12.800
ATOM	1365	C	GLY B	48	6.826 -8.512 13.141
ATOM	1366	0	GLY B	48	7.136 -7.832 14.149
ATOM	1367	N	GLY B	49	5.940 -8.027 12.306
ATOM	1368	H	GLY B	49	5.668 -8.562 11.506
ATOM	1369	CA	GLY B	49	5.336 -6.745 12.493
MOTA	1370	С	GLY B	49	4.082 -6.786 11.674 3.561 -7.847 11.273
ATOM	1371	0	GLY B	49	
MOTA	1372	N	ILE B	50	
MOTA	1373	H	ILE B	50	
MOTA	1374	CA	ILE B	50	
MOTA	1375	С	ILE B	50	2.11
ATOM	1376	0	ILE B	50	1.1/5
MOTA	1377	CB	ILE B	50	
ATOM	1378	CG1	ILE B	50	
MOTA	1379	CG2	ILE B	50	1.010
MOTA	1380	CD1	ILE B	50	0.510
ATOM	1381	N	GLY B	51	3.113 -6.410 8.519 3.957 -5.920 8.737
MOTA	1382	H	GLY B	51	2.926 -7.075 7.259
MOTA	1383	CA	GLY B	51	3.671 -8.391 7.077
ATOM	1384	C	GLY B	51	3.716 -8.945 5.973
ATOM	1385	0	GLY B	51 52	4.296 -8.982 8.116
ATOM	1386	N	GLY B	52 52	4.227 -8.580 9.029
MOTA	1387	H	GLY B	52 52	5.053 -10.190 7.874
MOTA	1388	CA	GLY B	52	6 334 -10.178 8.678
ATOM	1389	С	GLY B	52	6.519 -9.421 9.657
MOTA	1390	0	GLY B	52 53	7.325 -11.015 8.343
MOTA	1391	N	PHE B	53 ⁻	7.227 -11.603 7.540
ATOM	1392	H	PHE B	53	8.542 -11.096 9.110
MOTA	1393	CA	PHE B	53 53	9.727 -10.584 8.315
MOTA	1394	C	PHE B	53	9.780 -10.618 7.075
MOTA	1395	O	PHE B	53	8 804 -12.555 9.542
MOTA	1396		PHE B	53	7.850 -13.023 10.592
ATOM	1397			53	6.513 -13.277 10.279
MOTA	1398	נעט			•

FIG. I IY

		3	9/46	•
		:	53	8.279 -13.192 11.918
ATOM		CD2 PHE B	53	5.620 -13.697 11.253
MOTA		CE2 PHE B	53	7.382 -13.615 12.903
MOTA		CZ PHE B	53	6.052 -13.868 12.574
MOTA		N ILE B	54	10.758 -10.126 8.985
MOTA		H ILE B	54	10.005
MOTA MOTA		CA ILE B	54	12.023
ATOM		C ILE B	54	13.005
ATOM		O ILE B	54	12.332
ATOM		CB ILE B	54	12.390 -8.444 8.236 12.386 -7.775 9.611
ATOM	1409	CG1 ILE B	54	11.460 -7.770 7.218
ATOM		CG2 ILE B	54	13.113 -6.438 9.590
MOTA		CD1 ILE B	54	14.272 -10.852 8.523
MOTA		N LYS B	55	14.383 -10.599 7.562
MOTA	·	H LYS B	55 55	15 403 -11.431 9.216
MOTA	1414	CA LYS B	55	16 274 -10.324 9.732
MOTA	1415	C LYS B	55	16 620 -9.328 9.047
ATOM	1416		55	16.222 -12.237 8.245
MOTA	1417		55	15.638 -13.596 8.063
MOTA	1418	CG LYS B	55	16.299 -14.348 6.953
MOTA	1419	CE LYS B	55	15.311 -14.520 5.813
MOTA	1420 1421	NZ LYS B	55	15.757 -15.577 4.897
MOTA		HZ LYS B	55	15.095 -15.676 4.154
ATOM		HZ LYS B	55	15.830 -16.441 5.395 16.650 -15.334 4.518
MOTA MOTA		2HZ LYS B	55	10.030
ATOM	1425	N VAL B	56	10.000
ATOM	1426	H VAL B	56	10.,
ATOM	1427	CA VAL B	56	17.732 -9.578 11.534 18.884 -10.304 12.184
ATOM	1428	C VAL B	56	18.884 -11.539 12.367
MOTA	1429	O VAL B		16 912 -8.819 12.609
MOTA	1430	CB VAL B		15 865 -7 943 11.921
MOTA	1431	CG1 VAL B		16.215 -9.788 13.599
ATOM	1432	_		19.958 -9.593 12.591
MOTA	1433	N ARG B H ARG B		20.030 -8.624 12.353
MOTA	1434 1435			21.050 -10.193 13.386
MOTA	1435			20.963 -9.608 14.804
ATOM ATOM	1437	O ARG E		20.814 -8.395 15.053 22.426 -9.873 12.817
ATOM	1438	CB ARG E		22.120
ATOM	1439	CG ARG E	57	22.00.
ATOM	1440	CD ARG F	57	41.02
ATOM	1441	NE ARG E		24.200
MOTA	1442	HE ARG		23.592 -11.323 9.250 25.392 -10.478 8.921
MOTA	1443	CZ ARG		26.337 -9.650 9.353
MOTA	1444	NH1 ARG		26.223 -9.171 10.224
MOTA	1445	2HH1 ARG I		27 163 -9.505 8.808
MOTA	1446	1HH1 ARG I		25.561 -11.104 7.760
MOTA	1447			26.392 -10.950 7.225
MOTA	1448	1HH2 ARG		24.857 -11.729 7.422
MOTA	1449	N GLN		20.997 -10.489 15.832
ATOM	1450 1451	H GLN		21.176 -11.456 15.650
ATOM ATOM		CA GLN		20.780 -10.072 17.206
ATOM				22.108 -9.886 17.882 22.918 -10.815 18.038
MOTA			B 58	22.918 -10.815 18.038

FIG. 1 IZ

			4	0/46	1
N TTOM	1455	CB (GLN B	58	20.051 -11.190 17.932
ATOM	1455 1456		GLN B	58	19.765 -10.845 19.366
ATOM	1450		GLN B	58	19.179 -12.003 20.112
MOTA	1457		GLN B	58	19.712 -12.472 21.101
MOTA	1459		GLN B	58	18.055 -12.476 19.623
ATOM			GLN B	58	17.598 -13.249 20.063
ATOM ATOM			GLN B	58	17.647 -12.066- 18.807
ATOM	1462		TYR B	59	22.416 -8.692 18.422
ATOM	1463		TYR B	59	21.788 -7.921 18.3F1
MOTA	1464		TYR B	59	23.631 -8.486 19.161
ATOM	1465		TYR B	59	23.244 -8.290 20.607
ATOM	1466		TYR B	59	22.178 -7.728 20.927
ATOM	1467		TYR B	59	24.387 -7.241 18.653
ATOM	1468		TYR B	59	24.271 -7.075 17.149
ATOM	1469		TYR B	59	23.045 -7.242 16.494
ATOM	1470		TYR B	59	25.385 -6.753 16.374
ATOM	1471		TYR B	59	22.939 -7.093 15.112
ATOM	1472	CE2	TYR B	59	25.291 -6.603 14.995
ATOM	1473		TYR B	59	24.068 -6.774 14.365
ATOM	1474	OH	TYR B	59	24.018 -6.620 13.010 24.926 -6.394 12.658
ATOM	1475	HH	TYR B	59	51.55
ATOM	1476	N	ASP B	60	
ATOM	1477	H	ASP B	60	21.002
MOTA	1478	CA	ASP B	60	
ATOM	1479	С	ASP B	60	
MOTA	1480	0	ASP B	60	23.02
MOTA	1481	CB	ASP B	60	23.703
MOTA	1482	CG	ASP B	60	22.000
MOTA	1483	OD1	ASP B	60	
ATOM	1484	OD2	ASP B	60	23.208 -12.126 23.273 24.156 -7.022 24.774
MOTA	1485	N	GLN B	61	23.252 -7.234 25.146
MOTA	1486	H	GLN B	61	25.011 -6.086 25.519
ATOM	1487	CA	GLN B	61	25.411 -4.866 24.746
MOTA	1488	C	GLN B	61 61	26.560 -4.382 24.832
MOTA	1489	0	GLN B	61	26.269 -6.763 26.028
ATOM	1490	CB	GLN B	61	26.020 -8.038 26.753
ATOM	1491	CG	GLN B	61	25 714 -7.766 28.185
MOTA	1492	CD	GLN B	61	24.572 -7.455 28.548
ATOM	1493	OE1 NE2	GLN B	61	26.744 -7.844 29.014
ATOM	1494 1495	1HE2	GLN B	61	26,620 -7.675 29.992
ATOM	1496	2HE2	GLN B	61	27.654 -8.073 28.669
MOTA	1497	N	ILE B	62	24.539 -4.257 23.933
ATOM	1498	H	ILE B	62	23.628 -4.648 23.801
MOTA MOTA	1499	CA	ILE B	62	24.878 -3.047 23.238
ATOM	1500	C	ILE B	62	24.571 -1.885 24.144
ATOM	1501	Ö	ILE B	62	23.515 -1.819 24.819
ATOM	1502	CB	ILE B	62	24.097 -2.922 21.912
ATOM	1502				24.310 -4.170 21.094
ATOM	1504		ILE B		24.568 -1.709 21.067
ATOM	1505		ILE B		25.794 -4.479 20.878
ATOM	1506		LEU B		25.485 -0.912 24.304
MOTA	1507		LEU B		26.403 -1.028 23.926
MOTA	1508		LEU B		25.192 0.322 25.015
ATOM	1509		LEU B	63	24.630 1.296 24.030
ATOM	1510		LEU B	63	25.239 1.658 22.995

FIG. I laa

WO 01/35316 PCT/US00/30863

		41	146			
		CB LEU B	63	26.436	0.5.	25.590
MOTA			63	26.186	2.2.	26.226
MOTA		CC	63	25.486		27.576
MOTA		CD1 LEU B	63	27.468	J	26.382
MOTA		N ILE B	64	23.492		24.358
ATOM		H ILE B	64	22.958		25.148 23.617
MOTA	1516 1517	CA ILE B	64	23.003		24.612
MOTA	1517	C ILE B	64	22.872		24.612 25.84 6
ATOM	1519	O ILE B	64	22.915		22.989
MOTA MOTA	1520	CB ILE B	64	21.634	2.701 1.521	22.029
ATOM	1521	CG1 ILE B	64	21.825	3.894	22.246
ATOM	1522	CG2 ILE B	64	20.982 20.593	1.096	21.260
ATOM	1523	CD1 ILE B	64	20.593	5.460	24.172
ATOM	1524	N GLU B	65	23.013	5.664	23.216
ATOM	1525	H GLU B	65	22.432	6.551	25.037
MOTA	1526	CA GLU B	65	21.242	7.194	24.373
ATOM	1527	C GLU B	65 65	21.312	7.729	23.257
MOTA	1528	O GLU B	65	23.497	7.615	25.131
MOTA	1529	CB GLU B	65	24.787	7.196	25.761
MOTA	1530	T -	65	25.694	8.385	26.076
MOTA	1531		65	25.170	9.510	26.311
MOTA	1532	OE1 GLU B OE2 GLU B	65	26.938	8.200	26.092
MOTA	1533	N ILE B	66	20.078	7.240	25.035 25.947
MOTA	1534 1535	H ILE B	66	20.010	6.835	24.462
MOTA	1536	CA ILE B	66	18.907	7.865	25.145
MOTA MOTA	1537	C ILE B	66	18.777	9.195 9.303	26.379
MOTA	1538	O ILE B	66	18.591	6.995	24.790
MOTA	1539	CB ILE B	66	17.713	5.583	24.335
ATOM	1540	CG1 ILE B	66	17.916 16.405	7.544	24.177
ATOM	1541	CG2 ILE B		16.888	4.677	24.884
ATOM	1542	CD1 ILE B		18.965	10.325	24.437
ATOM	1543	N CYS B		19.201	10.268	23.467
ATOM	1544	H CYS B	_	18.833	11.663	25.049
MOTA	1545	CA CYS B		19.637	11.781	26.319
MOTA	1546			19.235	12.400	27.328
MOTA	1547			17.387	12.023	25.319
MOTA	1548	CB CYS B		16.407	12.259	23.821
ATOM	1549 1550			20.830	11.180	26.383 25.604
ATOM ATOM	1551		_	21.158	10.646	27.558
MOTA	1552		68	21.654	11.288 10.185	28.584
MOTA	1553	C GLY F	3 68	21.464	10.185	29.606
ATOM	1554	O GLY F		22.174	9.255	28.425
ATOM	1555	N HIS E		20.513 19.924	9.282	27.618
ATOM	1556	H HIS		20.304	8.199	29.391
MOTA	1557			20.861	6.936	28.811
MOTA				20.589	6.560	27.647
MOTA			B 69	18.832	7.992	29.654
MOTA		, СБ ::-0	B 69	18.175	9.203	30.223
MOTA			_	17.504	9.195	31.435
ATOM			-	17.383	8.402	32.032 29.729
ATOM			B 69	18.122	10.470	_
ATOM ATOM				17.070	10.429 11.240	
ATOM			B 69	17.410	11.240	30.022

FIG. 1 lbb

			42	146			
ATOM ATOM ATOM ATOM ATOM ATOM ATOM ATOM	1578	H I CA I C I C CB CCB CCD CE NZ 1HZ 3HZ	LYS B	/46 70 70 70 70 70 70 70 70 70	21.751 22.025 22.326 21.386 20.627 23.613 24.694 25.739 27.048 26.948 27.821 26.725 26.230	6.217 6.512 5.020 3.854 3.725 4.678 5.655 5.524 6.090 7.548 7.940 7.874 7.828	29.499 30.414 28.945 29.145 30.120 29.663 29.379 30.444 30.011 30.000 29.711 30.919 29.363
MOTA			LYS B ALA B	71	21.512	2.849	28.284
ATOM	1580 1581		ALA B	71	22.141	2.934	27.512 28.432
MOTA MOTA	1582	CA	ALA B	71	20.762	1.630 0.576	27.805
MOTA	1583	С	ALA B	71	21.629 22.463	0.830	26.912
ATOM	1584	0	ALA B	71	19.452	1.726	27.737
MOTA	1585	CB	ALA B	71 72	21.547	-0.681	28.237
MOTA	1586	N	ILE B	72	20.864	-0.925	28.926
ATOM	1587	H CA	ILE B	72	22.424	-1.698	27.730
MOTA MOTA	1588 1589	C	ILE B	72	- - · ·	-2.938	27.462 28.330
ATOM	1590	ō	ILE B	72		-3.490 -1.999	28.330
MOTA	1591	CB	ILE B	72		-1.999	29.090
ATOM	1592	CG1	ILE B	72	24.322 24.442	-3.037	28.153
MOTA	1593	CG2	ILE B	72 72	25.374	-1.012	30.163
MOTA	1594	CD1	ILE B GLY B	72 73	21.609	-3.446	26.235
MOTA	1595 1596	N H	GLY B	73	22.204	-3.054	25.534
MOTA MOTA	1597	CA	GLY B	73	20.707	-4.545	26.062 24.663
ATOM	1598	C	GLY B	73	20.828	-5.084 -4.831	23.863
MOTA	1599	0	GLY B	73	21.754 19.856	-5.905	24.271
MOTA	1600	N	THR B	74 74	19.086	-6.088	24.882
MOTA	1601	H	THR B	74 74	19.869	-6.548	22.988
MOTA	1602	CA C	THR B	74	19.363	-5.590	21.931
MOTA	1603 1604		THR B	74	18.338	-4.870	22.053 23.074
ATOM ATOM	1605		THR B	74	19.011	-7.801	24.013
MOTA	1606		THR B	74	19.611	-8.683 -9.519	24.092
MOTA	1607	HG1	_	74	19.068 18.817	-8.496	21.705
MOTA	1608			74 75	20.028	-5.620	20.762
MOTA	1609		VAL B		20.835	-6.203	20.666
ATOM	1610		VAL B		19.630	-4.837	19.611
ATOM	1611 1612		VAL B		19.600	-5.771	18.426
MOTA MOTA	1613		VAL B		20.444	-6.673	18.230 19.395
MOTA	1614		VAL B	75	20.667	-3.712 -3.002	18.046
MOTA	1615	G CG1			20.473 20.679	-2.708	20.567
MOTA	1616				18.557	-5.647	17.565
ATOM	1617		LEU B		17.822	-5.000	17.767
MOTA	1618 1619		LEU E		18.444	-6.427	16.324
ATOM ATOM	1620		LEU E		18.736	-5.487	15.144 15.040
ATOM	162		LEU E	3 76	18.239	-4.343 -7.021	
ATOM	162		LEU E	76	17.028	- / . 021	

FIG. I lcc

43/46

		15	T D	76	16.427	-7.612	17.449
MOTA	1623		U B	76 76	14.992	-8.075	17.263
MOTA	1624	CD1 LE		76 76	17.266	-8.758	18.019
MOTA	1625	CD2 LE			19.607	-5.900	14.222
ATOM	1626		LB	77	19.985	-6.824	14.276
MOTA	1627	•	LB	77	20.027	-5.042	13.133
MOTA	1628		LB	77	19.570	-5.662 ⁻	11.842
ATOM	1629	-	L B	77	19.570	-6.883	11.598
MOTA	1630	o VA		77	21.563	-4.905	13.191
ATOM	1631	CB VA		77		-4.202	11.944
ATOM	1632	CG1 VA		77	22.129 22.030	-4.166	14.470
ATOM	1633	CG2 VA		77	18.978	-4.915	10.943
ATOM	1634	N GL		78	18.978	-3.941	11.121
ATOM	1635	H GL		78		-5.475	9.705
ATOM	1636	CA GL		78	18.523	-4.338	8.874
ATOM	1637	C GI		78	18.019	-3.142	9.223
MOTA	1638	O GI		78	18.130	-4.596	7.722
ATOM	1639	N PR		79	17.408	-3.535	6.834
ATOM	1640	CA PR		79	16.954	-2.872	7.280
ATOM	1641	C PF		79	15.635	-2.877	6.565
ATOM	1642	O PF		79	14.609	-4.274	5.492
ATOM	1643	CB PF	O B	79	16.804	-5.712	5.881
ATOM	1644		O B	79	16.463	-5.712	7.189
ATOM	1645	CD PI	O B	79	17.159	-2.247	8.458
ATOM	1646	N ŢI	IR B	80	15.574	-2.247	9.058
MOTA	1647	H T	IR B	80	16.374	-2.242	8.865
ATOM	1648	CA T	IR B	80	14.364	-0.189	8.228
ATOM	1649	C T	R B	80	14.312	0.471	8.001
ATOM	1650	O T	HR B	80	15.349	-1.512	10.410
MOTA	1651	CB T	HR B	80	14.250	-0.802	10.806
ATOM	1652	OG1 T	HR B	80	13.079	-0.802	11.804
MOTA	1653	HG1 T	HR B	80	13.022	-0.766	11.062
ATOM	1654	CG2 T	HR B	80	15.519	0.354	7.885
ATOM	1655		RO B	81	13.137	1.747	7.379
ATOM	1656	CA P	RO B	81	13.036	2.732	8.484
ATOM	1657	C P	RO B	81	13.363	3.880	8.250
ATOM	1658		RO B	81	13.791	1.912	6.982
ATOM	1659	CB P	RO B	81	11.548	0.674	7.488
ATOM	1660		RO B	81	10.819	-0.387	7.797
ATOM	1661		RO B	81	11.854	2.368	9.772
ATOM	1662		AL B	82	13.197	1.427	9.992
MOTA	1663		AL B	82	12.940	3.306	10.885
MOTA	1664		AL B	82	13.380	2.668	12.010
MOTA	1665	_	AL B	82	14.160 14.045	1.465	12.293
MOTA	1666		AL B	82		3.695	11.431
ATOM	1667		AL B	82	11.996	4.961	12.269
MOTA	1668		AL B	82	12.055	3.857	10.318
MOTA	1669		AL B	82	10.958	3.422	12.775
ATOM	1670		asn b	83	14.963	4.370	12.516
ATOM	1671		ASN B		15.147	2.846	13.967
ATOM	1672		ASN B		15.550	2.874	15.022
ATOM	1673		ASN B		14.481 13.814	3.903	15.294
MOTA	1674		ASN B			3.639	14.472
ATOM	1675		ASN B		16.743 17.935	3.574	13.570
ATOM	1676		ASN B			2.511	13.167
ATOM	1677		ASN B		18.409 18.439	4.735	
ATOM	1678	ND2	ASN B			1.755	

FIG. 1 ldd SUBSTITUTE SHEET (RULE 26)

44/46 12.638 4.786 19.237 83 2HD2 ASN B MOTA 1679 13.582 5.580 18.030 1HD2 ASN B 83 1680 MOTA 1.749 15.711 14.225 ILE B 84 1681 N ATOM 0.938 15.564 14.791 ILE B 84 1682 Η MOTA 16.667 1.658 13.154 ILE B 84 CA 1683 MOTA 18.020 1.317 13.740 ILE B 84 C 1684 MOTA 0.300-18.223 ILE B 14.428 84 0 1685 MOTA 16.260 12.214 0.517 84 ILE B CB 1686 MOTA 14.849 0.759 11.656 CG1 ILE B 84 MOTA 1687 17.315 0.247 11.128 CG2 ILE B 84 1688 **ATOM** 14.291 -0.359 10.770 84 CD1 ILE B 1689 MOTA 19.051 2.157 13.483 85 ILE B N MOTA 1690 18.877 3.030 13.028 ILE B 85 1691 Η ATOM 20.408 13.846 1.834 85 ILE B 1692 CA MOTA 21.085 1.254 12.596 85 ILE B 1693 C MOTA 1.903 21.267 11.536 85 0 ILE B ATOM 1694 21.137 3.115 14.308 85 ILE B 1695 CB MOTA 20.395 3.826 15.447 85 CG1 ILE B 1696 ATOM 22.589 2.840 14.673 CG2 ILE B 85 1697 MOTA 20.263 3.053 16.730 CD1 ILE B 85 1698 ATOM . 21.422 12.617 -0.052 GLY B 86 N 1699 MOTA -0.595 21.251 13.439 86 GLY B 1700 Н MOTA 22.028 -0.702 11.481 GLY B 86 CA 1701 MOTA 23.538 -0.748 11.557 GLY B 86 C 1702 MOTA 24.238 -0.165 12.412 GLY B 86 0 1703 ATOM 24.149 -1.489 10.614 ARG B 87 N 1704 MOTA 23.604 -2.072 10.012 ARG B 87 1705 Н MOTA 25.584 -1.46810.442 ARG B 87 CA 1706 MOTA 26.326 -2.021 11.627 87 ARG B 1707 C ATOM 27.495 -1.666 11.911 ARG B 87 0 MOTA 1708 25.949 -2.271 9.200 87 ARG B MOTA 1709 CB 25.161 -1.960 7.951 87 ARG B 1710 CG **ATOM** 25.219 -3.074 6.956 87 ARG B CD 1711 **ATOM** 24.205 -2.933 5.906 87 ARG B MOTA 1712 NE -2.039 23.772 5.790 87 ARG B 1713 HE MOTA -3.953 23.856 5.119 ARG B 87 1714 CZATOM 24.396 -5.161 5.252 NH1 ARG B 87 1715 MOTA 25.085 -5.326 5.958 87 2HH1 ARG B 1716 MOTA -5.905 24.113 4.646 87 1HH1 ARG B 1717 MOTA -3.751 22.939 4.180 NH2 ARG B 87 1718 MOTA 22.664 -4.502 3.580 1719 1HH2 ARG B 87 MOTA 22.524 -2.8484.073 87 1720 2HH2 ARG B MOTA -2.937 25.731 12.413 88 AŞN B 1721 N MOTA -3.237 24.800 12.206 88 ASN B MOTA 1722 Н 26.415 -3.519 13.582 88 ASN B CA ATOM 1723 26.821 -2.42914.532 88 ASN B MOTA 1724 C -2.516 27.863 15.214 88 ASN B 0 MOTA 1725 25.559 -4.605 14.285 ASN B 88 1726 CB ATOM 24.358 -4.031 15.063 ASN B 88 MOTA 1727 CG 23.612 -3.24514.515 88 OD1 ASN B ATOM 1728 24.180 -4.445 16.333 ND2 ASN B 88 1729 MOTA 23.414 -4.099 16.875 2HD2 ASN B 88 MOTA 1730 -5.102 24.812 16.744 1HD2 ASN B 88 1731 ATOM -1.328 26.061 14.695 LEU B 89 N MOTA 1732 -1.240 25.201 14.192 89 LEU B H MOTA 1733 -0.234 26.452 15.597 LEU B 89 CA MOTA 1734

FIG. I lee substitute sheet (RULE 26)

			۷۲	5/46			
» TOM	1735	C 1	LEU B	89	14.797	0.937	27.053
ATOM ATOM	1736	_	LEU B	89	15.293	1.734	27.879 25.236
ATOM	1737		LEU B	89	16.421	0.232	24.567
MOTA	1738		LEU B	89	17.400	-0.754 0.002	23.573
ATOM	1739		LEU B	89	18.215	-1.458	25.570
ATOM	1740		LEU B	89	18.352 13.511	1.114~	26.705
ATOM	1741		LEU B	90	13.082	0.486	26.056
MOTA	1742		LEU B	90 90	12.698	2.221	27.257
MOTA	1743		LEU B LEU B	90	12.537	2.060	28.751
ATOM	1744	_	LEU B	90	12.575	3.033	29.533
MOTA	1745 1746		LEU B	90	11.311	2.258	26.628
MOTA MOTA	1747		LEU B	90	11.232	2.730	25.168 24.642
MOTA	1748		LEU B	90	9.808	2.744	24.042
MOTA	1749	CD2	LEU B	90	11.831	4.105 0.843	29.271
ATOM	1750	N	THR B	91	12.315	0.055	28.663
ATOM	1751	H	THR B	91	12.218 . 12.210	0.634	30.699
ATOM	1752	CA	THR B	91	13.537	1.028	31.375
MOTA	1753	С	THR B	91	13.575	1.525	32.518
MOTA	1754	0	THR B	91 91	11.893	-0.843	31.028
MOTA	1755	CB	THR B	91	12.919	-1.676	30.504
ATOM	1756	OG1	THR B	91	12.722	-2.634	30.713
MOTA	1757	HG1 CG2	THR B	91	10.599	-1.285	30.418
MOTA	1758 1759	N CG2	GLN B	92	14.705	0.852	30.732
MOTA	1760	H	GLN B	92	14.707	0.497	29.797
MOTA	1761	CA	GLN B	92	15.920	1.190	31.433
MOTA	1762	C	GLN B	92	16.088	2.660	31.633 32.527
ATOM	1763	0	GLN B	92	16.807	3.137 0.680	30.682
MOTA	1764	CB	GLN B	92	17.127 17.076	-0.805	30.517
MOTA	1765	CG	GLN B	92	18.336	-1.314	29.900
MOTA	1766	CD	GLN B	92 92	19.394	-0.720	30.059
MOTA	1767	OE1	GLN B	92	18.221	-2.411	29.195
ATOM	1768	NE2 1HE2	GLN B	92	19.022	-2.813	28.751
ATOM	1769 1770	2HE2	GLN B	92	17.331	-2.856	29.095
MOTA MOTA	1771	N	ILE B	93	15.538	3.512	30.746
ATOM	1772	H	ILE B	93	15.016	3.153	29.972 30.899
ATOM	1773	CA	ILE B	93	15.693	4.937 5.549	31.698
ATOM	1774	C	ILE B	93	14.522	6.773	31.940
ATOM	1775	0	ILE B		14.438 15.981	5.657	29.548
MOTA	1776	CB	ILE B		14.746	5.718	28.619
MOTA	1777	CG1			17.223	5.060	28.874
ATOM	1778		_		14.946	6.734	27.488
MOTA	1779		GLY B		13.617	4.731	32.263
ATOM	1780 1781		GLY B		13.639	3.752	32.060
ATOM	1782		GLY B		12.594	5.224	33.170
MOTA MOTA	1783		GLY E		11.443	5.846	32.432 32.878
MOTA	1784		GLY E		10.766	6.803	32.876
ATOM	1785		CYS E		11.134	5.354 4.538	30.888
ATOM	1786	H	CYS E		11.603	5.969	30.381
MOTA	1787	CA	CYS E		10.134 8.750	5.512	30.764
ATOM	1788		CYS E		8.478	4.309	31.006
MOTA	1789		CYS E		10.456	5.643	_
MOTA	1790	CB	CYS E	, ,,			

FIG. 1 Iff

				_		0.426	6.512	27.764
MOTA	1791	SG		В	95	9.426 7.778	6.444	30.764
MOTA	1792	N		В	96		7.401	30.539
MOTA	1793	H	THR	В	96	8.014	6.163	31.108
MOTA	1794	CA	_	В	96	6.379	6.970	30.254
MOTA	1795	С		В	96	5.390	8.171	30.254
MOTA	1796	0	THR	В	96	5.567	6.439	32.604
MOTA	1797	CB		В	96	6.111		32.938
ATOM	1798	OG1	THR	В	96	6.341	7.794 7.924	33.861
MOTA	1799	HG1	THR	В	96	6.111	5.566	33.554
MOTA	1800	CG2	THR	В	96	6.938		29.809
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MOTA	1806	CB		В	97	2.226	5.958	28.532
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ATOM	1808	CD1	LEU	В	97	2.101	3.986	26.957
MOTA	1809	CD2	LEU	В	97	2.842	6.216	26.085
ATOM	1810	N	ASN	В	98	1.637	8.777	30.024
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MOTA	1813	C	ASN	В	98	-0.251	10.321	30.231
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MOTA	1815	CB .	ASN	В	98	1.845	10.678	31.587
MOTA	1816	CG		В	98	2.783	10.077	32.634
MOTA	1817	OD1	ASN	В	98	3.926	9.739	32.335
MOTA	1818	ND2	ASN	В	98	2.297	9.942	33.870
MOTA	1819	2HD2	ASN	В	98	2.877	9.551	34.599
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ATOM	1829	CD2	LEU	В	99	-5.134	7.943	29.528
MOTA	1830	OXT	LEU	В	99	-4.842	11.156	30.376
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FIG. I lgg

WO 01/35316 PCT/US00/30863

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                                                                                   48
  Pro Gln Ile Thr Leu Trp Gln Arg Pro Xaa Val Thr Ile Lys Ile Gly
  ggc caa cta aaa gaa gct yta tta gat aca gga gca gat gat aca gta
Gly Gln Leu Lys Glu Ala Xaa Leu Asp Thr Gly Ala Asp Asp Thr Val
                                                                                   96
                                        25
  tta gaa gaa atg agt tta cca ggg aaa tgg aaa cca aaa atg ata ggg
Leu Glu Glu Met Ser Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly
                                                                                  144
  gga att gga ggt ttt atc aaa gta aga cag tat gat caa ata ctc ata
                                                                                  192
  Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Leu Ile
                               55
  gaa atc tgt gga cat aaa gct ata ggc aca gta tta gta gga cct aca
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-3-

	lu 65	Ile	Cys	Gly	His	Lys 70	Ala	Ile	Gly	Thr	Val 75	Leu	Val	Gly	Pro	Thr 80		
P	ro	gtc Val	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ttg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr	28	18
_ t	ta eu	aat Asn	ttg Leu	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	33	6
						cca Pro											38	4
a L	aa ys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	gga Gly	43	2
L	aa ys 45	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gag Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	ata Ile	ttt Phe 160	48	0
g A	cc la	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	52	8
						aga Arg											57	6
a I	ta le	cca Pro	cac His 195	ccc Pro	gca Ala	gly ggg	tta Leu	aaa Lys 200	cag Gln	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	ata Ile	ctg Leu	62	4
g: A:	at sp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gaa Glu	ggc Gly	ttc Phe	agg Arg	. 67	2
L	ag ys 25	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	aga Arg	aat Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	72	0
at I	tt le	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aac Asn	gtg Val	ctc Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	76	8
						agc Ser											81	6
						gtt Val											86	4
G.	ĹУ	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	gga Gly 295	cag Gln	cat His	aga Arg	gca Ala	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	91	2
aç	ga	gga	cat	cta	tta	aag	tgg	gga	ttt	acc	aca	cca	gac	aaa	aaa	cat	96	0

	Arg 305	Gly	His	Leu	Leu	Lys 310	Trp	Gly	Phe	Thr	Thr 315	Pro	Asp	Lys	Lys	His 320	
	cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttt Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
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	<211 <212	0> 4 L> 10 2> DI 3> Hi	NA.	Immi	ınod:	ific	iency	/ Vii	rus	(HIV)	ı						
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	<222	•	298).	(1 on of	-		erse	e Tra	ansci	ripta	ıse						
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	ggg Gly	cag Gln	cta Leu	aag Lys 20	gaa Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
	gtt Val	gaa Glu	gaa Glu 35	atg Met	aat Asn	ttg Leu	cca Pro	gga Gly 40	aaa Lys	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	Gly 999	144
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	gaa Glu 65	aty Xaa	tgt Cys	gga Gly	cat His	aga Arg 70	gct Ala	atg Met	ggt Gly	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
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	tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
	cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
	aaa	ata	aaa	gca	tta	ġta	gaa	atc	tgt	aca	gaa	ttg	gaa	aag	gaa	999	432

-5-

	Lys	Ile 130		Ala	Leu	Val	Glu 135		Cys	Thr	Glu	Leu 140		Lys	Glu	Gly	
		Ile				999 Gly 150	Pro					Asn					480
-11						aac Asn											528
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						agc Ser											816
						gtt Val											864
						ata Ile											912
2						aag Lys 310											960
Ć	cag Gln	aaa Lys	gaa Glu	cct Pro	cct Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	ccc Pro 335	gat Asp	1008
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-6-

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-7-

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aag ~~Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	ggg Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
cag Gln	aat Asn	cca Pro 275	gaa Glu	atg Met	gtc Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	gag Glu 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gat Asp	gaa Glu	ctg Leu	912
aga Arg 305	caa Gln	tat Tyr	ctg Leu	tgg Trp	aag Lys 310	tgg Trp	gga Gly	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aca Thr	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
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<222		298).		116) HIV	/ / Rev	/erse	e Tra	ansci	ripta	ase						
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-8-

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-9-

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caa aat cca gac Gln Asn Pro Asp 275	atg gtc atc tat caa Met Val Ile Tyr Gln 280	tac atg gat gat ttg Tyr Met Asp Asp Leu 285	tat gta 864 Tyr Val
gga tct gac tta Gly Ser Asp Leu 290	gaa ata gga cag cac Glu Ile Gly Gln His 295	aga aca aaa ata gag Arg Thr Lys Ile Glu 300	gaa ctg 912 Glu Leu
		acc aca cca gac aag Thr Thr Pro Asp Lys 315	
Gln Lys Glu Pro	cca ttc ctt tgg atg Pro Phe Leu Trp Met 325	ggt tat gaa ctc cat Gly Tyr Glu Leu His 330	cct gat 1008 Pro Asp 335
		cca gaa aaa gac agc Pro Glu Lys Asp Ser 350	
gtc aat gac ata Val Asn Asp Ile (355	cag aag tta gtg gga Gln Lys Leu Val Gly 360	aaa tta aat tgg gca Lys Leu Asn Trp Ala 365	agt cag 1104 Ser Gln
att tac cca ggg Ile Tyr Pro Gly 370			1116
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<221> CDS [.] <222> (298)(11 <223> Portion of	116) HIV Reverse Transcr	iptase	
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ggg caa cta aag g Gly Gln Leu Lys G 20	gaa gct cta tta gat a Blu Ala Leu Leu Asp ' 25	aca gga gca gat gat a Thr Gly Ala Asp Asp 30	aca gta 96 Thr Val
tta gag gaa atn a Leu Glu Glu Xaa A	at tta cca gga aga i sn Leu Pro Gly Arg 1	ngg aaa cca aaa atg a Trp Lys Pro Lys Met I	ata ggg 144 Ile Gly

-10-

			33	•				40	,				4.5	•			
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_		Xaa		gga Gly			Āla					Leu				aca Thr 80	240
	Pro	gtc Val	aac Asr	ata Ile	att Ile 85	Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	Thr	caa Gln	att Ile	ggt Gly	tgc Cys 95	Thr	288
	tta Leu	aat Asn	ttt Phe	Pro	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
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				gca Ala													720
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	caa Gln	aat Asn	cca Pro	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp	ttg Leu	tat Tyr	gta Val	864

-11-

275		280	285	
		Gln His Arg Thr I	aaa ata gag gaa ctg 91 Lys Ile Glu Glu Leu 300	12
			cca gac aaa aaa cat 96 Pro Asp Lys Lys His 320	50
Gln Lys Glu Pro 1			gaa ctc cat cct gat 100 Glu Leu His Pro Asp 335	8
aaa tgg aca gta o Lys Trp Thr Val (340	cag cct ata Gln Pro Ile	gtg ctg cca aca a Val Leu Pro Thr I 345	aaa gac agc tgg act 105 Lys Asp Ser Trp Thr 350	66
			aac tgg gca agt cag 110 Asn Trp Ala Ser Gln 365	4
att tat gca ggg Ile Tyr Ala Gly 370			111	.6
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<221> CDS <222> (298)(11 <223> Portion of		Transcriptase		
Pro Gln Ile Thr L			ca gta aag ata ggg 4 hr Val Lys Ile Gly 15	8
ggg caa ata aag g	aa oot vta 1			
Gly Gin lie Lys G 20	lu Ala Xaa	tta gat aca gga go Leu Asp Thr Gly A 25	ca gat gat aca gta 90 la Asp Asp Thr Val 30	6
20 tta gaa gaa atg a	at ttg cca	Leu Asp Thr Gly A 25 gga aga tgg aaa co	la Asp Asp Thr Val	
tta gaa gaa atg a Leu Glu Glu Met A 35 gga att gga ggt t	at ttg cca g sn Leu Pro G	Leu Asp Thr Gly A 25 gga aga tgg aaa co Gly Arg Trp Lys Pr 40 gta aga cag tat ga Val Arg Gln Tyr As	la Asp Asp Thr Val 30 ca aaa ata ata ggg 144 ro Lys Ile Ile Gly	4

-12-

65					70					75					80	•
cct Pro	gtc Val	aat Asn	ata Ile	att Ile 85	Gly	aga Arg	aat Asn	ctg Leu	atg Met 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr	288
tta Leu		ttt Phe														336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc	cca Pro	aga Arg	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
		aaa Lys														432
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	ggc Gly	agt Ser	aac Asn	aga Arg	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
		ctt Leu														576
		cat His 195														624
		ggt Gly														672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	aca Thr	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
		tat Tyr														768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
		cca Pro 275														864
		gac Asp														912
aga Arg		cat His														960

WO 01/35316 PCT/US00/30863

-13-

305	310	315	320
		ggt tat gaa ctc cat Gly Tyr Glu Leu His 330	
aaa tgg aca gta cag Lys Trp Thr Val Gln 340	cct ata gtg ctg Pro Ile Val Leu 345	cca gar aaa gac agc Pro Glu Lys Asp Ser 350	tgg act 1056 Trp Thr
gtc aat gac ata cag Val Asn Asp Ile Gln 355	aag tta gtg gga Lys Leu Val Gly 360	aaa ttg aat tgg gca Lys Leu Asn Trp Ala 365	agt caa 1104 Ser Gln
att tac cca ggg Ile Tyr Pro Gly 370			1116
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<220> <221> CDS <222> (0)(297) <223> HIV Protease			
<221> CDS <222> (298)(1116) <223> Portion of HIV		iptase	
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ggg caa cta aag gaa Gly Gln Leu Lys Glu 20	gct cta tta gat Ala Leu Leu Asp 25	aca gga gca gat gat Thr Gly Ala Asp Asp 30	aca gta 96 Thr Val
tta gaa gaa atg aat Leu Glu Glu Met Asn 35			
gga att gga ggt ttt Gly Ile Gly Gly Phe 50			
gaa atc tgt gga cat Glu Ile Cys Gly His 65			
cct gtc aac ata atw Pro Val Asn Ile Xaa 85			
tta aat ttt ccc att			tta aag 336

-14-

			100					105					110			
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	ata Ile	gaa Glu 135	att Ile	tgt Cys	aca Thr	gag Glu	atg Met 140	gag Glu	aag Lys	gaa Glu	GJA aaa	432
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aaa Lys	act Thr	caa Gln	gay Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	car Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	gta Val	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	ggg Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aag Lys 265	atc Ile	tta Leu	gar Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gaa Glu	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tcw Xaa 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	caa Gln	cat His	aga Arg	ata Ile	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	cag Gln	cat His	ctg Leu	tta Leu	agg Arg 310	tgg Trp	Gly 999	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggk Xaa 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu	cca Pro	gaa Glu	aaa Lys	gay Asp	agc Ser	tgg Trp	act Thr	1056

-15-

			340					345					350			
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
		cca Pro														1116
<21:	0> 10 L> 13 2> Di 3> Hu	L16 NA	Immi	ınod:	ific	iency	y Vi:	rus	(HIV)	•						
<222	L> CI 2> (()).,	. (29' rote:			•								-		
<222		298)	(: on of		V Rev	verse	e Tra	ansci	ripta	ase						
cct)> 10 cag Gln	atc	act Thr	ctt Leu 5	tgg Trp	caa Gln	cga Arg	ccc Pro	ctc Leu 10	gtc Val	aca Thr	gta Val	aag Lys	ata Ile 15	gly aaa	48
Gly 999	caa Gln	ata Ile	aag Lys 20	gaa Glu	gct Ala	yta Xaa	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
tta Leu	gaa Glu	gaa Glu 35	atg Met	aat Asn	ttg Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atw Xaa	ata Ile	GJA aaa	144
gga Gly	att Ile 50	gga Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	cag Gln	gta Val	ccc Pro	ata Ile	192
gaa Glu 65	atc Ile	tgt Cys	gga Gly	caa Gln	aaa Lys 70	gct Ala	ata Ile	agt Ser	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
cct Pro	gtc Val	aat Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	atg Met 90	Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	cct Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	taa *	aag Lys	336
cca Pro	gga Gly	atg Met	gat Asp 115	ggc Gly	cca Pro	aga Arg	gtt Val	aaa Lys 120	caa Gln	tgg Trp	cca Pro	ttg Leu	aca Thr 125	gaa Glu	gaa Glu	384
aaa Lys	ata Ile	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu	atc Ile	tgt Cys	aca Thr	gaa Glu	atg Met	gaa Glu	aag Lys	gaa Glu	Gly ggg	432

-16-

		130					135					140				
aaa Lys	att Ile 145	tca Ser	aaa Lys	att Ile	Gly 999	cct Pro 150	gaa Glu	aat Asn	cca Pro	tac Tyr	aat Asn 155	act Thr	cca Pro	gta Val	ttt Phe	480
gcc -Ala 160	ata Ile	aag Lys	aaa Lys	aaa Lys	ggc Gly 165	agt Ser	aac Asn	aga Arg	tgg Trp	aga Arg 170	aaa Lys	tta Leu	gta Val	gat Asp	ttc Phe 175	528
aga Arg	gaa Glu	ctt Leu	aat Asn	aag Lys 180	aaa Lys	act Thr	caa Gln	gac Asp	ttc Phe 185	tgg Trp	gaa Glu	gtt Val	caa Gln	tta Leu 190	gga Gly	576
ata Ile	cca Pro	cat His	ccc Pro 195	gca Ala	ggg Gly	cta Leu	aaa Lys	aag Lys 200	aaa Lys	aaa Lys	tca Ser	gta Val	aca Thr 205	gta Val	ctg Leu	624
gat Asp	gtg Val	ggt Gly 210	gat Asp	gca Ala	tat Tyr	ttt Phe	tca Ser 215	gtt Val	ccc Pro	tta Leu	gat Asp	aaa Lys 220	gaa Glu	ttc Phe	agg Arg	672
aag Lys	tat Tyr 225	act Thr	gca Ala	ttt Phe	acc Thr	ata Ile 230	cct Pro	agt Ser	aca Thr	aac Asn	aat Asn 235	gag Glu	aca Thr	cca Pro	Gly 999	720
att Ile 240	aga Arg	tat Tyr	cag Gln	tac Tyr	aat Asn 245	gtg Val	ctt Leu	ccm Xaa	caa Gln	gga Gly 250	tgg Trp	aaa Lys	Gly 999	tca Ser	cca Pro 255	768
gca Ala	ata Ile	ttc Phe	caa Gln	agt Ser 260	agc Ser	atg Met	aca Thr	aaa Lys	atc Ile 265	tta Leu	gag Glu	cct Pro	ttt Phe	aga Arg 270	aaa Lys	816
caa Gln	aat Asn	cca Pro	gac Asp 275	wtr Xaa	gtt Val	atc Ile	tat Tyr	caa Gln 280	tac Tyr	atg Met	gat Asp	gat Asp	ttg Leu 285	tat Tyr	gta Val	864
agc Ser	tct Ser	gac Asp 290	tta Leu	gaa Glu	ata Ile	ggg Gly	cag Gln 295	cat His	aga Arg	aca Thr	aaa Lys	ata Ile 300	gag Glu	gaa Glu	cta Leu	912
aga Arg	caa Gln 305	cat His	ctg Leu	ttg Leu	agg Arg	tgg Trp 310	gga Gly	tta Leu	acc Thr	aca Thr	cca Pro 315	gac Asp	aaa Lys	aaa Lys	cat His	960
cag Gln 320	aaa Lys	gaa Glu	cct Pro	cca Pro	ttc Phe 325	ctt Leu	tgg Trp	atg Met	ggt Gly	tat Tyr 330	gaa Glu	ctc Leu	cat His	cct Pro	gat Asp 335	1008
aaa Lys	tgg Trp	aca Thr	gta Val	cag Gln 340	cct Pro	ata Ile	gtg Val	ctg Leu	cca Pro 345	gag Glu	aaa Lys	gac Asp	agc Ser	tgg Trp 350	act Thr	1056
gtc Val	aat Asn	gac Asp	ata Ile 355	cag Gln	aag Lys	tta Leu	gtg Val	gga Gly 360	aaa Lys	ttg Leu	aat Asn	tgg Trp	gca Ala 365	agt Ser	caa Gln	1104
	tac Tyr															1116

-17-

370

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<221> CDS <222> (298)(1116) <223> Portion of HIV Reverse Transcriptase	
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ggg caa cta aaa raa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Xaa Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa atg ata gtg Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Val 35 40 45	144
gga att gga ggt ttt gtc aaa gta aga cag tat gat cag gta ccc ata Gly Ile Gly Gly Phe Val Lys Val Arg Gln Tyr Asp Gln Val Pro Ile 50 55 60	192
gag atc tgt ggg cat aaa att ata ggt aca gta tta ata gga cct acc Glu Ile Cys Gly His Lys Ile Ile Gly Thr Val Leu Ile Gly Pro Thr 65 70 75 80	. 240
cct gcc aac gta att gga aga aat ctg atg act cag ctt ggt tgc act Pro Ala Asn Val Ile Gly Arg Asn Leu Met Thr Gln Leu Gly Cys Thr 85 90 95	288
tta aat ttt ccc att agt yct att gaa act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Xaa Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336
CCa gga atg gat ggc cCa aaa gtt aaa caa tgg cCa ttg aCa gaa gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta gta gaa att tgt gca gaa ctg gag aag gaa ggg Lys Ile Lys Ala Leu Val Glu Ile Cys Ala Glu Leu Glu Lys Glu Gly 130 135 140	432
aaa att tca aga att ggg cct gaa aat cca tac aat act cca ata ttt Lys Ile Ser Arg Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Ile Phe 145 150 155 160	480
gcc ata aag aag aaa aac agt act agg tgg aga aaa tta gta gat ttc Ala Ile Lys Lys Lys Asn Ser Thr Arg Trp Arg Lys Leu Val Asp Phe	528

-18-

				165					170					175		
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	taa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	att Ile	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	cct Pro	gca Ala	gly ggg	tta Leu	aaa Lys 200	aag Lys	aac Asn	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggg Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	tac Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	aca Thr	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	caa Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	gat Asp	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gat Asp	ccc Pro	ttt Phe 270	aga Arg	aag Lys	816
aaa Lys	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	yta Xaa	gaa Glu	ata Ile	gag Glu 295	cag Gln	cat His	aga Arg	gca Ala	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	gaa Glu	tat Tyr	ctg Leu	tta Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	ttc Phe	aca Thr 315	cca Pro	gag Glu	caa Gln	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggc Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gtg Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aag Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aac Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
_	tac Tyr 370						·									1116

<210> 12 <211> 1116 <212> DNA <213> Human Immunodificiency Virus (HIV)

-19-

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 <222> (0)...(297)
 <223> HIV Protease
 <221> CDS
 <222> (298)...(1116)
--<223> Portion of HIV Reverse Transcriptase
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 Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly
                                           10
 ggg caa cta aag gaa gcc cta tta gat aca gga gca gat gat aca gta
                                                                                 96
 Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val
                                                                                144
 cta gaa gaa atg aat ttg cca gga aaa tgg aaa cca aaa atg ata ggg
 Leu Glu Glu Met Asn Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly
 gga att gga ggt ttt atc aaa gta agg cag tat gat car ata ccc ata
                                                                                192
 Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Pro Ile
 gag atc tgc ggg tat aaa gct gtg ggt aca gta tta gta gga cct aca
Glu Ile Cys Gly Tyr Lys Ala Val Gly Thr Val Leu Val Gly Pro Thr
                                                                                240
 cct gtc aac ata att gga aga aat ctg ttg act caa att ggt tgc act
                                                                                288
 Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr
 tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
                                                                                336
               100
 cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa
                                                                                384
 Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu
                                 120
                                                                                432
 aaa ata aaa gca tta ata gaa att tgt aca gaa atg gaa aag gaa gga
 Lys Ile Lys Ala Leu Ile Glu Ile Cys Thr Glu Met Glu Lys Glu Gly
 aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt
                                                                                480
 Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
                                                                     160
 145
                        150
 gcc ata aag aaa aaa gac ggt act aaa tgg aga aaa tta gta gat ttc
                                                                                528
 Ala Ile Lys Lys Lys Asp Gly Thr Lys Trp Arg Lys Leu Val Asp Phe
                                                                                576
 aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtt caa tta gga
 Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly
                                      185
 ata cca cat ccc gca ggg tta aaa aag aaa aaa tca gta aca gta cta
Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu
                                                                                624
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-20-

	195					200					205				
Asp V	tg ggt al Gly 10	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	caa Gln	gac Asp	ttc Phe	aga Arg	672
aag t Lys T 225	at act yr Thr	gca Ala	ttc Phe	act Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
att ag Ile A	ga tat rg Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca at Ala I	ta ttc le Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa aa Gln As	at cca sn Pro 275	gac Asp	atg Met	gtt Val	atc Ile	tat Tyr 280	caa Gln	tat Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
Gly Se	ct gac er Asp 90	tta Leu	gaa Glu	aya Xaa	999 Gly 295	cag Gln	cat His	aga Arg	rca Xaa	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga ca Arg Gl 305	aa cat ln His	ctg Leu	ttg Leu	agg Arg 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag aa Gln Ly	aa gaa ys Glu	cct Pro	cca Pro 325	ttt Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa to Lys Ti	gg aca rp Thr	gta Val 340	cag Gln	cct Pro	ata Ile	atg Met	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
	at gac sn Asp 355														1104
	at gca yr Ala 70														1116
<210> <211> <212> <213>	1116	Immu	modi	.fici	.ency	, Vir	rus ((HIV)							
	CDS (0) HIV Pr								•						
	CDS (298). Portic			' Rev	erse	: Tra	ınscr	ripta	se						

-21-

	4.0		_														
	cct	0> 1: cag Gln	atc	act Thr	ctt Leu 5	tgg Trp	caa Gln	cga Arg	ccc Pro	aty Xaa 10	gtc Val	aac Asn	ata Ile	aag Lys	gta Val 15	Gly 999	48
1	ggg Gly	caa Gln	cta Leu	arg Xaa 20	gaa Glu	gct Ala	cta Leu	ata Ile	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
	tta Leu	gaa Glu	gac Asp 35	ata Ile	gat Asp	ttg Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aga Arg	cca Pro	aga Arg 45	atg Met	ata Ile	Gly	144
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	gaa Glu 65	ata Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gtt Val	ata Ile	ggt Gly	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	acg Thr 80	240
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	ata Ile	ccg Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	tta Leu	ara Xaa 200	aag Lys	aaa Lys	aga Arg	tca Șer	gta Val 205	aca Thr	gta Val	ctg Leu	624
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	aag Lys 225	tat Tyr	act Thr	gcc Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	ggg Gly 240	720

PCT/US00/30863

-22-

						•								
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ggg caa Gly Gln	Val Ar	g gaa g Glu 0	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96

-23-

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			ggc Gly														192
gaa Glu 65	atc Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gct Ala	ata Ile	Gly 999	aca Thr	gtg Val 75	tta Leu	ata Ile	gga Gly	cct Pro	aca Thr 80		240
			ata Ile														288
			cct Pro 100														336
cca Pro	gga Gly	atg Met 115	gat Asp	ggt Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu		384
			gca Ala														432
			aaa Lys													-	480
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			aat Asn 180														576
			ccc Pro														624
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			gca Ala														720
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			caa Gln 260												aag Lys		816

WO 01/35316 PCT/US00/30863

-24-

									Gln					Leu		gta Val	864
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									cta Leu 345								1056
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1	tta : Leu :	kaa (Xaa (gaa Glu 1 35	atg Met	gat Asp	ttg Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	gly ggg	144
ć	gga Bly	att (Ile (50	gga (Gly (ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	cag Gln	gta Val	tcc Ser	wta Xaa	192

-25-

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					cca Pro											384
					gta Val											432
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					ggg Gly											624
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					acc Thr 230											720
					aat Asn											768
					agc Ser											816
					gtt Val											864
					ata Ile											912

WO 01/35316 PCT/US00/30863

-26-

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cag aaa Gln Lys													Asp	1008
aaa tgg Lys Trp		Gln												1056
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50				55										
gaa atc t Glu Ile C 65	gt gga			gct					tta					240

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	cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
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	aag Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
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	ata Ile	cca Pro	cat His 195	cct Pro	gca Ala	Gly Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aag Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
	gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gaa Glu	gac Asp	ttc Phe	agg Arg	672
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	gca Ala	ata İle	ttc Phe	caa Gln 260	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aag Lys	816
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												cca Pro					960
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-28-

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Gly ggg	caa Gln	cta Leu	aag Lys 20	gaa Glu	gcc Ala	cta Leu	ata Ile	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gtg Val	96
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cct Pro	gcc Ala	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr	288
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ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	999 Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
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-30-

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						atc Ile											192
						aaa Lys 70											240
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			Phe			agt Ser											336
						ccg Pro											384
	aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	Gly ggg	432
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-31-

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                                                                                   96
ggg caa cta acg gaa gct yta ttg gat aca gga gca gat aat aca gta
Gly Gln Leu Thr Glu Ala Xaa Leu Asp Thr Gly Ala Asp Asn Thr Val
tta gaa gaa atg agt ttr cca gga aga tgg aaa cca aaa atg ata ggg
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Leu Glu Glu Met Ser Xaa Pro Gly Arg Trp Lys Pro Lys Met Ile Gly
gga att gga ggt ttt atc aaa gta aga cag tat gat cag ata ccc ata
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Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Pro Ile
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Glu Ile Cys Gly His Lys Val Val Gly Thr Val Leu Ile Gly Pro Thr
                                               . 75
cct gtc aac ata att gga aga gat ctg ttg act cag att ggt tgc act
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Pro Val Asn Ile Ile Gly Arg Asp Leu Leu Thr Gln Ile Gly Cys Thr
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Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
                                      105
              100
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu
                                                                                  384
aaa ata aaa gca tta gta gaa att tgt aca gaa ctg gaa aag gaa ggg
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Glu Gly
                                                                                  432
    130
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
                                                                                  480
                        150
                                                                                  528
gcc ata aag aaa aar gac agt act aaa tgg aga aaa ttr gta gat ttc
Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Xaa Val Asp Phe
                                                                                  576
aga gaa ctt aat aaa aga act caa gac ttc tgg gaa gtt caa tta gga
Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly
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-33-

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	Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttc Phe 215	tca Ser	gtt Val	ccc Pro	cta Leu	gat Asp 220	aaa Lys	gaa Glu	ttc Phe	agg Arg	672
1	aag Lys 225	tat Tyr	act Thr	gca Ala	ttc Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	gta Val	aac Asn 235	aat Asn	gag Glu	act Thr	cca Pro	999 Gly 240	720
;	att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctg Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
3	gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
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. (gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	gta Val	gag Glu	gaa Glu	ctg Leu	912
7	aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	Gly aaa	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
(cag Gln	aaa Lys	gaa Glu	ccc Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
ā	aaa Lys	tgg Trp	aca Thr	gtg Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	Asp	agc Ser 350	tgg Trp	act Thr	1056
Ç	gtc Val	aat Asn	gac Asp 355	ata Ile	caa Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
	_	tac Tyr 370	_	==-													111,6
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•	<222	L> CI ?> (())	. (29°													

-34-

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WO 01/35316 PCT/US00/30863

-35-

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att aga tat caa Ile Arg Tyr Gln				
gca ata ttt caa Ala Ile Phe Gln 260	Cys Ser Met			
gaa aat cca gat Glu Asn Pro Asp 275				864
gga tct gat tta Gly Ser Asp Leu 290		Gln His Arg		
aga caa tat ctg Arg Gln Tyr Leu 305				960
cag caa gaa cct Gln Gln Glu Pro				1008
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gat tta tgc agg Asp Leu Cys Arg 370	g			1117
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-36-

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	tta Leu	gaa Glu	gac Asp 35	atg Met	cat His	ttg Leu	cca Pro	ggt Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	gtg Val	144
	gga Gly	att Ile 50	ggg Gly	ggt Gly	ttt Phe	gtc Val	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	cag Gln	ata Ile	cct Pro	gta Val	192
	gaa Glu 65	atc Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gct Ala	ata Ile	ggt Gly	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
	cca Pro	gcc Ala	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr	288
	tta Leu	aat Asn	ttc Phe	ccc Pro 100	atc Ile	agt Ser	cct Pro	att	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
	cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	att Ile 120	aga Arg	caa Gln	tgg Trp	cca Pro	tta Leu 125	aca Thr	gaa Glu	gaa Glu	384
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	aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
	gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	aat Asn	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
,	aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
	ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	gly ggg	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	cta Leu	624
	gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
	aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	atg Met	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	gga Gly 240	720
														gga Gly			768

-37-

gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agt Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
 Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtc Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	Asp	gat Asp 285	tta Leu	tat Tyr	gta Val	864
gga Gly	tcg Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	ggg Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ttg Leu	912
aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	aga Arg 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gtg Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aag Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtt Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	caa Gln	1104
	tat Tyr 370															1116
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<222	0> L> CI 2> (0 3> HI))														
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ggg Gly	caa Gln	cta Leu	aag Lys 20	gag Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
tta Leu	gaa Glu	gac Asp 35	ata Ile	gat Asp	ttg Leu	cca Pro	gga Gly 40	agr Xaa	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	gly ggg	144

-38-

gga	att	gga	aat	ttt	atc	aaa	gta	aga	cag	tat	gat	cag	ata	ccc	ata	192
ĞÎş	Ile 50	Gly	Gly	Phe	Ile	Lys 55	Val	Arg	Gln	Tyr	Asp 60	Gln	Ile	Pro	Ile	
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ect	gtc Val	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cgg Arg	att Ile	ggt Gly	tgc Cys 95	act Thr	288
tta Lev	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	gga Gly	432
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gcc Ala	ata	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttt Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gat Asp 185	ttc Phe	tgg Trp	gaa Glu	gtg Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	ccg Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aar Lys	gay Asp	ttc Phe	agg Arg	672
aag Lys 225	tat Tyr	act Thr	gcc Ala	Phe	acc Thr 230	Ile	cct Pro	Ser	ata Ile	Asn	Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tat Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	cta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	atg Met	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864

WO 01/35316 PCT/US00/30863

-39-

Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu 290 295 300	912 1
aga gaa cat ctg ttg agg tgg gga ttt acc acc cca gac aaa aaa cat Arg Glu His Leu Leu Arg Trp Gly Phe Thr Thr Pro Asp Lys Lys His 305 310 315	1
cag aaa gag cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008
aaa tgg acc gtr cag cct ata gag ctg cca gaa aaa gac agc tgg act Lys Trp Thr Xaa Gln Pro Ile Glu Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350	1056
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Glr 355 360 365	1104
att tac cca ggg Ile Tyr Pro Gly 370	1116
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<222> (0)(297) <223> HIV Protease <221> CDS <222> (298)(1116)	48
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-40-

						gga Gly												288
_					Ile	agt Ser									Leu			336
				Asp		cca Pro												384
			Lys			aca Thr												432
						999 Gly 150												480
						aat Asn												528
						aga Arg												576
						gga Gly												624
						tat Tyr												672
						acc Thr 230												720
						aat Asn												768
						agc Ser												816
	caa Gln	aat Asn	cca Pro 275	gaa Glu	ata Ile	gtt Val	atc Ile	tgt Cys 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val		864
						ata Ile												912
	aga Arg 305					agg Arg 310											:	960

-41-

Caq Gl:	g aaa n Lys	a gaa s Glu	a cct a Pro	cca Pro 325	Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	Tyr	gaa Glu	ctc Leu	cat His	cct Pro	gat Asp	1008
aaa Lys	a tgg s Trp	g aca Thr	gta Val 340	Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	Pro	gaa Glu	aar Lys	gac Asp	agt Ser 350	Trp	acw Xaa	1056
gty Xaa	z aat a Asn	gac Asp 355	Ile	cag Gln	aaa Lys	tta Leu	gtk Xaa 360	Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	Ala	agt Ser	caa Gln	1104
		Pro	Gly													1116
<21 <21	.0> 2 .1> 1 .2> D .3> H	116 NA	Imm	unodi	ific	ienc	y Vi	rus	(HIV)						
<22	1> C 2> (0)	.(29 rotea										•			
<22		298)	(1 on of			verse	e Tra	ansc	ripta	ase						
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Gly 999	Caa Gln	cta Leu	aag Lys 20	gaa Glu	gct Ala	cta Leu	ata Ile	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
tta Leu	gaa Glu	gac Asp 35	ata Ile	aat Asn	ttg Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	Lys	tta Leu	ata Ile	Gly 999	144
												45				
gga Gly	att Ile 50	gga Gly	ggt Gly	ttt Phe	gtc Val	aga Arg 55	gtg	aaa Lys	cag Gln	tat Tyr	gat Asp 60	caq	ata Ile	ccc Pro	ata Ile	192
Gly	Ile 50 att	Gly	ggt Gly gga Gly	Phe cat	Val aaa	Arg 55 gtt	gtg Val ata	Lys ggt	Gln	Tyr gta	Asp 60 tta	cag Gln gta	Ile gga	Pro	Ile	192 240
gaa Glu 65 cct	Ile 50 att Ile gcc	tgt Cys	Gly gga	Phe cat His	Val aaa Lys 70 gga	Arg 55 gtt Val aga	gtg Val ata Ile	Lys ggt Gly ctg	Gln aca Thr	Tyr gta Val 75	Asp 60 tta Leu cag	cag Gln gta Val	Ile gga Gly	Pro cct Pro	aca Thr 80	

PCT/US00/30863

			Āsp					Lys					Thr		gaa Glu	384
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	Ile			att Ile							Asn					480
gcy Xaa	ata Ile	cac His	aag Lys	aaa Lys 165	aat Asn	agt Ser	aat Asn	aga Arg	tgg Trp 170	Arg	aaa Lys	gta Val	gta Val	gat Asp 175	ttc Phe	528
				aag Lys												576
				gca Ala												624
				gca Ala												672
				ttt Phe												720
atc Ile	aga Arg	tac Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	caa Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
				agt Ser										Arg		816
				ata Ile							Asp					864
				gaa Glu												912
				ttg Leu												960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys		Thr														1056

-43-

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ggg caa cta aag gaa gct cta cta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gaa atg agt ttg cca gga aaa tgg aaa cca aaa atg ata ggg Leu Glu Glu Met Ser Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly 35 40 45	144
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gaa atc tgt gga cat aaa gtt ata ggt aca gta tta gta gga tct aca Glu Ile Cys Gly His Lys Val Ile Gly Thr Val Leu Val Gly Ser Thr 65 70 75 80	240
cct gtc aac ata att gga aga aat ytg ttg act cag ctt ggg tgc act Pro Val Asn Ile Ile Gly Arg Asn Xaa Leu Thr Gln Leu Gly Cys Thr 85 90 95	288
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta ata gaa att tgt aca gaa atg gaa aag gar ggg Lys Ile Lys Ala Leu Ile Glu Ile Cys Thr Glu Met Glu Lys Glu Gly 130 135 140	432

-44-

	: Ile					Pro					Asn				ttt Phe 160	480
gcc	ata Ile	aag Lys	aaa Lys	aaa Lys 165	Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	Arg	aag Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	Lys	aaa Lys	act Thr	caa Gln	gat Asp 185	ttc Phe	tgg Trp	gaa Glu	rtt Xaa	caa Gln 190	Ļeu	gga Gly	576
		cat His 195											Thr		ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtc Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
	Tyr	act Thr														720
		tat Tyr														768
gca Ala	ata Ile	ttc Phe	caa Gln 260	tat Tyr	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tac Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	gaa Glu 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
		cat His														960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctc Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gtt Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aag Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
		cca Pro														1116

-45-

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Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Glu Ile Lys Val Gly
                                                                                      48
 ggg caa cta ata gaa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Ile Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val
                                                                                      96
 tta gaa gaa ata aat tta cca gga aga tgg aaa cca aga atg ata ggg
                                                                                     144
 Leu Glu Glu Ile Asn Leu Pro Gly Arg Trp Lys Pro Arg Met Ile Gly
 gga att gga ggt ttt gtc aaa gta aga cag tat gat cag gta cct atc
                                                                                     192
 Gly Ile Gly Gly Phe Val Lys Val Arg Gln Tyr Asp Gln Val Pro Ile
 gaa atc tgt gga cat aaa gtt ata agt aca gta tta gta gga cct aca
                                                                                     240
 Glu Ile Cys Gly His Lys Val Ile Ser Thr Val Leu Val Gly Pro Thr
 ect gee aac ata att gga aga aat etg atg aet eag att ggt tge aet
                                                                                     288
 Pro Ala Asn Ile Ile Gly Arg Asn Leu Met Thr Gln Ile Gly Cys Thr
 tta aat ttt cct att agt cct att gaa act gta cca gta aaa tta aaa
                                                                                     336
 Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
               100
 cca gga atg gat ggc cca aga gtt aaa caa tgg cca ttg aca gaa gaa
                                                                                    384
 Pro Gly Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu
aaa ata aaa gca tta gta gaa att tgt aca gaa ytg gaa gag gaa ggg
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Xaa Glu Glu Glu Gly
                                                                                    432
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca ata ttt
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Ile Phe
                                                                                    480
                                                155
gcc ata aag aag aaa nnn agt ggt aga tgg aga aaa ata gta gat ttt
                                                                                    528
Ala Ile Lys Lys Lys Xaa Ser Gly Arg Trp Arg Lys Ile Val Asp Phe
                   165
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-46-

	aga Arg	gaa Glu	ctt Leu	aat Asn 180	Lys	aga Arg	act Thr	caa Gln	gat Asp 185	Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	Leu	gga Gly	576
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			ggt Gly														672
	aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aat Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
	att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
	gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
	caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	cag Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
	gga Gly	tct Ser 290	gat Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	gag Glu	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
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1	aaa Lys	tgg Trp	aca Thr	gta Val 340	cas Xaa	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gat Asp	agc Ser 350	tgg Trp	act Thr	1056
Ş	gtc /al	Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
	le '		cca Pro														1116

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WO 01/35316 PCT/US00/30863

-47-

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-48-

gtg Val	ggt Gly 210	gat Asp	gca Ala	tat Tyr	ttt Phe	tca Ser 215	gtt Val	ccc Pro	tta Leu	gat Asp	aag Lys 220	gaa Glu	ttc Phe	agg Arg	aag Lys	672
 tat Tyr 225	act Thr	gca Ala	ttt Phe	acc Thr	ata Ile 230	cct Pro	agt Ser	ata Ile	aat Asn	aat Asn 235	gag Glu	aca Thr	cca Pro	Gly 999	att Ile 240	720
aga Arg	tat Tyr	cag Gln	tac Tyr	aat Asn 245	gtg Val	ctt Leu	cca Pro	cag Gln	gga Gly 250	tgg Trp	aaa Lys	gga Gly	tca Ser	cca Pro 255	gca Ala	768
ata Ile	ttc Phe	caa Gln	agt Ser 260	agc Ser	atg Met	aca Thr	aaa Lys	atc Ile 265	tta Leu	gag Glu	cct Pro	ttt Phe	aga Arg 270	aaa Lys	caa Gln	816
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tct Ser	gat Asp 290	tta Leu	gaa Glu	ata Ile	Gly 999	gag Glu 295	cat His	aga Arg	aca Thr	aaa Lys	ata Ile 300	gag Glu	gaa Glu	ctg Leu	aga Arg	912
car Gln 305	cat His	ctg Leu	tta Leu	arg Xaa	tgg Trp 310	gga Gly	ttt Phe	ttc Phe	aca Thr	cca Pro 315	gaa Glu	caa Gln	aaa Lys	cat His	cag Gln 320	960
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tgg Trp	aca Thr	gta Val	cas Xaa 340	cct Pro	ata Ile	gtg Val	ctg Leu	cca Pro 345	gaa Glu	aaa Lys	gat Asp	agc Ser	tgg Trp 350	act Thr	gtc Val	1056
aat Asn	gac Asp	ata Ile 355	cag Gln	aag Lys	tta Leu	gtg Val	gga Gly 360	aaa Lys	ttg Leu	aat Asn	tgg Trp	gca Ala 365	agt Ser	cag Gln	att Ile	1104
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-49-

cct	00 > 2 caa	ato	act	stt	t tgg	, caa	cga	ccc	aty	gtc	: tca	ata	aag	ata	ggg	48
Pro 1	o Gln	ı Ile	: Thr	Xaa 5	a Trp	Gln	. Arg	Pro	Xaa 10		Ser	: Ile	. Lys	Ile 15	Gly	
G1 ⁷	g caa g Gln	ata Ile	a aag Lys 20	Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	Thr	gta Val	96
tta Leu	gaa Glu	gaa Glu 35	Met	aat Asn	ttg Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aag Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	gtg Val	144
gga Gly	att Ile 50	Gly	ggt Gly	ttt Phe	agc Ser	aaa Lys 55	gta Val	aga Arg	caa Gln	tat Tyr	gat Asp 60	Gln	ata Ile	ccc Pro	ata Ile	192
gaa Glu 65	Ile	tgc Cys	gga Gly	cgt Arg	aaa Lys 70	gtt Val	gta Val	ggt Gly	tca Ser	gta Val 75	tta Leu	ata Ile	gga Gly	cct Pro	aca Thr 80	240
cct Pro	gcc Ala	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	ctt Leu	ggc Gly	tgt Cys 95	act Thr	288
					agt Ser											336
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aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	ata Ile	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	ttg Leu 140	gaa Glu	gaa Glu	gma Xaa	gga Gly	432
aaa Lys 145	att Ile	aca Thr	aaa Lys	att Ile	150 Gly 999	cct Pro	gaa Glu	aat Asn	ccg Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	ata Ile	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aar Lys 165	aac Asn	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gac Asp 175	ttc Phe	528
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aar Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	Thr	aat Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720

PCT/US00/30863

-50-

	att Ile	aga Arg	tat Tyr	cag Gln	tat Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
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	aga Arg 305	caa Gln	cat His	ctg Leu	tgg Trp	aag Lys 310	tgg Trp	gga Gly	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
	cag Gln	aaa Lys	gaa Glu	ccc Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
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	gtc Val	aat Asn	gac Asp 355	ata Ile	caa Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
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	gly ggg	caa Gln	cta Leu	aag Lys 20	gaa Glu	gct Ala	cta Leu	ata Ile	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96

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÷	tta Leu	gaa Glu	gaa Glu 35	atg Met	aat Asn	ttg Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	ata Ile	ata Ile	Gly aaa	144
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	cct Pro	gcc Ala	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	ctt Leu	ggt Gly	tgc Cys 95	act Thr	288
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	cca Pro	gly ggg	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
	aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gag Glu	aag Lys	gag Glu	gga Gly	432
	aag Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
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	ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	ggg ggg	tta Leu	aaa Lys 200	aag Lys	aac Asn	aaa Lys	tca Ser	gca Ala 205	aca Thr	gta Val	ctg Leu	624
	gat Asp	gtg Val 210	ggc Gly	gat Asp	gca Ala	Tyr	Phe	Ser	Val	Pro	Leu	gac Asp 220	ьys	gaa Glu	ttc Phe	agg Arg	672
	aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acy Xaa 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gaa Glu	aca Thr	cca Pro	999 Gly 240	720
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	gca Ala	ata Ile	ttc Phe	maa Xaa 260	agt Ser	agc Ser	atg Met	aca Thr	aga Arg 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816

-52-

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Ğly											aaa Lys 300					912
aga Arg 305																960
cag (Gln)																1008
aaa 1 Lys 1																1056
gtc a Val i																1104
att t Ile :	tac Tyr 370	gcn Ala	gly ggg													1116
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Gly G																96
tta g Leu G	gaa g Slu (gaa a Glu I 35	atg Met	agc Ser	tta Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	gly aaa	144
gga a Gly I	le (gga g Sly 1	ggk Kaa	ttt Phe	atc Ile	aaa Lys 55	gtg Val	agm Xaa	cag Gln	tat Tyr	gat Asp 60	cag Gln	ata Ile	ctc Leu	ata Ile	192

-53-

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												cca Pro					336
												cca Pro					384
												atg Met 140					432
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												aaa Lys					528
												gaa Glu					576
												tca Ser					624
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												aat Asn					720
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												gat Asp					864
	Gly											aaa Lys 300					912

-54-

Arg Gln His 305	ctg ttg ag Leu Leu Ar 31	g Trp Gly E	ttc tac aca Phe Tyr Thr 315	Pro Asp Ly	aa aaa cat ys Lys His 320	960
cag aaa gaa Gln Lys Glu	cct cca tt Pro Pro Ph 325	c ctt tgg a e Leu Trp M	atg ggt tat Met Gly Tyr 330	gaa ctc ca Glu Leu Hi	at cct gat is Pro Asp 335	1008
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gtc aat gac Val Asn Asp 355	ata cag aa Ile Gln Ly	g tta gta g s Leu Val G 360	ggg aaa tta Gly Lys Leu	aat tgg go Asn Trp Al 365	a agt cag La Ser Gln	1104
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<222> (298) <223> Portice <400> 31 cct cag atc Pro Gln Ile	act ctt tg Thr Leu Tr 5 aag gaa gc	g caa cga c p Gln Arg F t cta tta g	ccc ctc gtc Pro Leu Val 10 gat aca gga	Thr Ile Ly gca gat gat Ala Asp As	rs Ile Gly 15 nt aca gta	· 48
<222> (298) <223> Portion <400> 31 cct cag atc Pro Gln Ile 1	act ctt tg Thr Leu Tr 5 aag gaa gc Lys Glu Al 20 gtg cat tt	g caa cga c p Gln Arg F t cta tta g a Leu Leu A	ccc ctc gtc Pro Leu Val 10 gat aca gga Asp Thr Gly 25	Thr Ile Ly gca gat gat Ala Asp As cca aaa at	rs Ile Gly 15 at aca gta p Thr Val 10 g ata ggg	
<222> (298) <223> Portice <400> 31 cct cag atc Pro Gln Ile 1 ggg caa tta Gly Gln Leu cta gaa gac Leu Glu Asp	act ctt tg Thr Leu Tr 5 aag gaa gc Lys Glu Al 20 gtg cat tt Val His Le	g caa cga cop Gln Arg F t cta tta g a Leu Leu A g cca gga a u Pro Gly I 40 c aaa gta a	ccc ctc gtc Pro Leu Val 10 gat aca gga Asp Thr Gly 25 aaa tgg aaa Lys Trp Lys	gca gat ga Ala Asp As Cca aaa at Pro Lys Me 45 gat gag gt	at aca gta properties of the second s	96
<222> (298) <223> Portice <400> 31 cct cag atc Pro Gln Ile 1 ggg caa tta Gly Gln Leu cta gaa gac Leu Glu Asp 35 gga att gga Gly Ile Gly	act ctt tg Thr Leu Tr 5 aag gaa gc Lys Glu Al 20 gtg cat tt Val His Le ggt ttt at Gly Phe Il	g caa cga cgo Go Gln Arg F t cta tta ga Leu Leu A g cca gga a u Pro Gly I 40 c aaa gta a e Lys Val A 55	ccc ctc gtc Pro Leu Val 10 gat aca gga Asp Thr Gly 25 aaa tgg aaa Lys Trp Lys aga cag tat Arg Gln Tyr	gca gat ga Ala Asp As cca aaa at Pro Lys Me 45 gat gag gt Asp Glu Va 60 tta gta gg Leu Val Gl	at aca gta thr Val ag ata ggg the Gly accc ata al Pro Ile	96 144

-55-

	cta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
	cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
	aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	Gly aaa	432
	aaa Lys 145	att Ile	tca Ser	aga Arg	gtt Val	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
	gyc Xaa	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
	aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
	ata Ile	cca Pro	cay His 195	ccc Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctr Xaa	624
	gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gaa Glu	ttc Phe	aga Arg	672
	aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
	att Ile	aga Arg	tac Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	caa Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
	gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gat Asp	cct Pro	ttt Phe 270	agg Arg	aaa Lys	816
	caa Gln	aac Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
	gga Gly	tcy Xaa 290	Asp	tta Leu	gaa Glu	ata Ile	gga Gly 295	cag Gln	cat His	agr Xaa	rca Xaa	aaa Lys 300	ata Ile	gaa Glu	gaa Glu	ctg Leu	912
	aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aag Lys	aaa Lys	cat His 320	960
-	car Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttt Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008

-56-

aaa tgg aca Lys Trp Thr	gtg cag Val Gln 340	cct ata Pro Ile	gtg ctg Val Leu 345	cca gaa Pro Glu	aag gac Lys Asp	agc to Ser Tr 350	g act p Thr	1056
gtc aat gac Val Asn Asp 355	Xaa Thr	gaa gtt Glu Val	agt ggg Ser Gly 360	aaa att Lys Ile	gaa ttg Glu Leu 365	ggc aa Gly Ly	g tca s Ser	1104
gat tta tgo Asp Leu Cys 370				·	·			1117
<210> 32 <211> 1116 <212> DNA <213> Human	Immunod	ificienc	y Virus	(HIV)				
<220> <221> CDS <222> (0) <223> HIV F		·					·	
<221> CDS <222> (298) <223> Porti			e Transc	riptase				
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ggg caa cta Gly Gln Leu	aag gaa Lys Glu 20	gcc cta Ala Leu	tta gat Leu Asp 25	aca gga Thr Gly	gca gat Ala Asp	gat ac Asp Th	a gta r Val	96
tta gaa gac Leu Glu Asp 35	Met Glu	ttg cca Leu Pro	gga aga Gly Arg 40	tgg aag Trp Lys	cca aaa Pro Lys 45	atg at Met I]	a ggg e Gly	144
gga att gga Gly Ile Gly 50	ggt ttt Gly Phe	atc aaa Ile Lys 55	gta aam Val Xaa	cag tat Gln Tyr	gat cag Asp Gln 60	ata ct Ile Le	t gta u Val	192
gaa atc tgt Glu Ile Cys 65	Gly His	aaa gct Lys Ala 70	Val Gly	Thr Val	Leu Ile	gga co Gly Pr	t aca to Thr 80	240
cct gtc aac Pro Val Asn	ata att Ile Ile 85	gga aga Gly Arg	aat ttg Asn Leu	ttg act Leu Thr 90	cag att Gln Ile	GTA C	c act s Thr	288
tta aat ttt Leu Asn Phe	ccc att Pro Ile 100	agt cct Ser Pro	att gaa Ile Glu 105	act gta Thr Val	cca gta Pro Val	aaa tt Lys Le 110	a aag u Lys	336
cca gga atg Pro Gly Met 115	Asp Gly	cca aaa Pro Lys	gtt aaa Val Lys 120	caa tgg Gln Trp	cca ttg Pro Leu 125	aca ga	a gag u Glu	384

-57-

a. L	ys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	atc Ile	tgt Cys	aca Thr	gaa Glu	ttg Leu 140	gaa Glu	aag Lys	gaa Glu	gga Gly	432
aa Ly 14	ys	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
9¢	ct la	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
									gac Asp 185								576
at II	a le :	cca Pro	cat His 195	ccc Pro	gca Ala	Gly 999	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tcc Ser	gtg Val 205	aca Thr	gta Val	ctg Leu	624
ga As	p '	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttt Phe	aga Arg	672
aa Ly 22	/S 1	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	aya Xaa	cct Pro	sgt Xaa	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
at Il	t a	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tcc Ser 255	cca Pro	768
									aaa Lys 265								816
ca Gl	a a .n /	aat Asn	cca Pro 275	gac Asp	wta Xaa	gtt Val	wtc Xaa	tat Tyr 280	caa Gln	twc Xaa	ata Ile	gat Asp	gat Asp 285	ctg Leu	tat Tyr	gta Val	864
gg G1	y S	set Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
Ar	a d g (3ln	His	Leu	Trp	Lys	Trp	Gly	ttt Phe	Tyr	Thr	Pro	Asp	Lys	Lys	cat His 320	960
									atg Met								1008
aa Ly	a t	rp gg	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	atg Met	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gt Va	c a l A	Asn .	gac Asp 355	ata Ile	cag Gln	aar Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104

WO 01/35316 PCT/US00/30863

-58-

att tac cca ggg Ile Tyr Pro Gly 370	1116
<210> 33 <211> 1116 <212> DNA <213> Human Immunodificiency Virus (HIV)	
<220> <221> CDS <222> (0)(297) <223> HIV Protease	
<221> CDS <222> (298)(1116) <223> Portion of HIV Reverse Transcriptase	
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ggg caa cta aag gaa gct cta tta kat aca gga gca gat gat aca gtm Gly Gln Leu Lys Glu Ala Leu Leu Xaa Thr Gly Ala Asp Asp Thr Xaa 20 25 30	96
tta gaa gac atg act ttg cca gga aga tgg aaa cca aaa atg ata ggg Leu Glu Asp Met Thr Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly 35 40 45	144
gga att gga ggt ttt atc aaa gta aaa cag tat gag gag ata ccc ata Gly Ile Gly Gly Phe Ile Lys Val Lys Gln Tyr Glu Glu Ile Pro Ile 50 55 60	192
gaa atc tgt gga cat aaa gct ata ggt aca gta tta gta gga cct aca Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr 65 70 75 80	240
cct gtc aac ata att gga aga aat ttg ttg act cag att ggt tgc act Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr 85 90 95	288
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aaa Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca ttw gta gaa att tgt gca gaa ctg gaa aag gaa ggg Lys Ile Lys Ala Xaa Val Glu Ile Cys Ala Glu Leu Glu Lys Glu Gly 130 135 140	432
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe 145 150 155 160	480

-59-

gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	ggt Gly	act Thr	aaa Lys	tgg Trp 170	aga Arg	aag Lys	gta Val	aca Thr	gat Asp 175	ttt Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	agg Arg	ach Xaa	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	tca Ser	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
	gtg Val 210															672
	tat Tyr															720
	aga Arg															768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
	aat Asn															864
	tct Ser 290															912
	caa Gln															960
	aaa Lys															1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
att Ile	tat Tyr 370	tca Ser	Gly 999													1116

<210> 34 <211> 1119 -60-

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<212> DNA
 <213> Human Immunodificiency Virus (HIV)
 <220>
 <221> CDS
 <222> (0)...(297)
<223> HIV Protease
 <221> CDS
 <222> (298)...(1119)
 <223> Portion of HIV Reverse Transcriptase
                                                                                     48
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 Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile Gly
                                             10
 ggg cag cta aag gaa gct cta ttr gac aca gga gca gat gat aca gta
                                                                                     96
 Gly Gln Leu Lys Glu Ala Leu Xaa Asp Thr Gly Ala Asp Asp Thr Val
                                                                                    144
 tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa ata ata ggg
 Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Ile Ile Gly
 gga att gga ggt ttt att aaa gta aaa cag tat gaa cag ata acc ata
                                                                                    192
 Gly Ile Gly Gly Phe Ile Lys Val Lys Gln Tyr Glu Gln Ile Thr Ile
 gam atc tgt gga cat aaa gct aca ggt aca gta tta gta gga cct aca
Xaa Ile Cys Gly His Lys Ala Thr Gly Thr Val Leu Val Gly Pro Thr
                                                                                    240
 cct gtc aac gta att gga aga aat atg atg act cag att ggt tgc act
Pro Val Asn Val Ile Gly Arg Asn Met Met Thr Gln Ile Gly Cys Thr
                                                                                    288
 tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag
                                                                                    336
 Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
                100
                                                                                    384
 cca gga atg gat ggc cca aga gtt aaa caa tgg cca ttg aca gaa gaa
 Pro Gly Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu
                                  120
           115
 aaa ata aaa gca tta gta gaa att tgt aca gaa ttg gaa aag gaa ggg
                                                                                    432
 Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Glu Gly
                                                                                    480
 aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt
 Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
                                                 155
                         150
 gcc ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc
Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe
                                                                                    528
                    165
 aga gaa ctt aac aag aga act caa gac ttc tgg gaa gtt caa tta gga
Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly
                                                                                    576
                180
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-61-

ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	gly aaa	tta Leu	cca Pro 200	aag Lys	aac Asn	aaa Lys	tca Ser	gta Val 205	acg Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	cct Pro	tta Leu	gat Asp 220	gaa Glu	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	tac Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agg Arg	tat Tyr	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
act Thr	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cct Pro	atg Met 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aga Arg	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gac Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gag Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	gcg Ala	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	gaa Glu	cat His	ctg Leu	tgg Trp	aag Lys 310	tgg Trp	ggt Gly	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	cat His	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aag Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aaa Lys	tta Leu	gtg Val 360	ggr Xaa	aaa Lys	att Ile	gaa Glu	ttt Phe 365	Gly	cga Arg	gtc Val	1104
			caa Gln													1119

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<212> DNA <213> Human Immunodificiency Virus (HIV)

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<221> CDS <222> (0)...(297) <223> HIV Protease

-62-

<221> CDS <222> (298) . . . (1115) <223> Portion of HIV Reverse Transcriptase 48 cct cag atc act ctt tgg caa cga ccc cty gtc cca ata arg ata ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Xaa Val Pro Ile Xaa Ile Gly 96 ggg caa tta aag gaa gct cta cta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val tta gaa gac atg aat tta cca gga aga tgg aaa cca aaa atg ata ggg Leu Glu Asp Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly 144 gga att gga ggt ttt atc aar gta aaa cag tat gat cag ata ccc ata Gly Ile Gly Gly Phe Ile Lys Val Lys Gln Tyr Asp Gln Ile Pro Ile 192 50 240 gaa atc tgt ggg cat aaa gct ata ggt aca gta tta gta gga cct aca Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr 288 cct qtc aac ata att qqa aga aat ctg ttg act cag ctt ggt tgc act Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Leu Gly Cys Thr 336 cta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 105 384 cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 432 aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa gga Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly 130 aaa att tca aaa att gga cct gaa aat cca tac aat act cca gta ttt Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe 480 145 gcc ata aag aaa aag gac agt act aaa tgg aga aaa tta gta gat ttc 528 Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe 165 576 aga gaa ctt aat aag aga act caa gac ttt tgg gaa gtc caa tta gga Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly 185 624 ata cca cat ccc gca ggg tta aaa aag aaa aaa tca gta aca gta tta Ile Pro His Pro Ala Gly Leu Lys Lys Lys Ser Val Thr Val Leu gat gtg gga gat gca tat ttt tca gtt ccc tta gat aaa gac ttc agg 672 Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Asp Phe Arg 210 215

WO 01/35316 PCT/US00/30863

-63-

aa Ly 22	s Ty	t act r Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
at I]	t aga e Arg	a tat g Tyr	cag Gln	tac Tyr 245	Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gc Al	a ata a Ile	a ttc e Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aag Lys	816
ca G1	a aat .n Asi	cca Pro 275	gac Asp	ata Ile	gtc Val	ata Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gg G1	g tct y Sei 290	gac Asp	tta Leu	gaa Glu	ata Ile	gga Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
ag Ar 30	g Glr	cac His	ttg Leu	ttg Leu	maa Xaa 310	tgg Trp	gga Gly	ttc Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aag Lys	cat His 320	960
ca Gl	g aaa n Lys	gaa Glu	ccc Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aa Ly	a tgg s Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	kaa Xaa	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	ctg Leu	1056
t c Se	a ato r Met	aca Thr 355	tac Tyr	aga Arg	aat Asn	tag *	tgg Trp	gaa Glu 360	agt Ser	tga *	att Ile	ggg Gly	caa Gln	gtc Val 365	aaa Lys	1104
_	t atg e Met	cng Xaa	gg													1115
<2 <2	<210> 36 <211> 1116 <212> DNA <213> Human Immunodificiency Virus (HIV)															
<2 <2	20> 21> C 22> (23> H	DS 0) IV Pi	. (297 cotea	') ise												
<2		DS 298) ortic				erse	. Tra	nscr	ipta	ıse				٠		
CC	o Gln	6 atc Ile	act Thr	ctt Leu 5	tgg Trp	caa Gln	cga Arg	cca Pro	gtc Val 10	gtc Val	aca Thr	ata Ile	aag Lys	gta Val 15	ggg ggg	48

-64-

ć	31y 3gg	cag Gln	cta Leu	aag Lys 20	gaa Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
t 1	ta Leu	gaa Glu	gaa Glu 35	atg Met	aat Asn	ttg Leu	cca Pro	gga Gly 40	aga Arg	tġg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	Gly aaa	144
Ġ	gga 31y	att Ile 50	gga Gly	ggt Gly	ttt Phe	rtc Xaa	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	caa Gln	ata Ile	ccc Pro	ata Ile	192
Ć	gaa 31u 65	atc Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gct Ala	aca Thr	ggt Gly	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
3	ect Pro	gyc Xaa	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	gly ggg	tgc Cys 95	act Thr	288
1	tta Leu	aat Asn	ttt Phe	cct Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
. 1	cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ctg Leu 125	aca Thr	gaa Glu	gaa Glu	384
į	aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	gca Ala	gaa Glu	ttg Leu 140	gaa Glu	aag Lys	gaa Glu	gj aaa	432
1	aag Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	ccy Xaa	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aay Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
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i	aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gat Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
;	ata Ile	Pro	cat His 195	Pro	gca Ala	gly 999	Leu	Lys	Lys	Lys	ьув	Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
j	gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	ttg Leu	gat Asp 220	gaa Glu	gac Asp	ttc Phe	aga Arg	672
	aag Lys 225	tat Tyr	aca Thr	gcc Ala	ttt Phe	acc Thr 230	tat Tyr	act Thr	ggt Gly	tcc Ser	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
•	att Ile	aga Arg	tat Tyr	car Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768

WO 01/35316 PCT/US00/30863

-65-

gca ata ttc caa agc agc atg aca aaa gtc tta gaa cct ttt aga aaa Ala Ile Phe Gln Ser Ser Met Thr Lys Val Leu Glu Pro Phe Arg Lys 260 265 270	816													
caa aat cca gac ata gtt atc tgt caa tac atg gat gat ttg tat gta Gln Asn Pro Asp Ile Val Ile Cys Gln Tyr Met Asp Asp Leu Tyr Val 275 280 285	864													
gga tct gac tta gaa ata ggg cag cat aga aca aaa ata gag gaa ctg Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu 290 295 300	912													
aga caa cat ctg tta agg tgg gga ttt tac aca cca gac gaa aaa cat Arg Gln His Leu Leu Arg Trp Gly Phe Tyr Thr Pro Asp Glu Lys His 305 310 315 320	960													
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gac Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008													
aaa tgg aca gta cag cct ata gtg ctg cca gaa aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350	1056													
gtt aat gac ata cag aaa tta gtg gga aaa ttg aat tgg gcc agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104													
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ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96													
tta gaa gac atg aat ttg cca gga aga tgg aaa cca aaa atg ata ggg Leu Glu Asp Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly 35 40 45	144													

-66-

gg G1	a at y Il 5	e Gl	a gg y Gl	t tt y Ph	t ato e İle	c aaa Lys 55	₹Va]	a aga L Arg	a cag g Glr	g tai	t gat r Asp 60	Glr	g gta	a cco l Pro	c ata o Ile	192
ga Gl 6	u Il	c tg e Cy	t gg s Gl	a cat y His	t aaa s Lys 70	. Ala	ata Ile	a ggt e Gly	aca Thr	gta Val	l Let	a gta 1 Val	a gga	a cct	aca Thr 80	240
cc Pr	t gt o Vai	c aa l As	c ata n Ila	a att e Ile 89	e Gly	aga Arg	aat Asn	ctg Leu	atg Met 90	Thr	a cag	g ctt Leu	ggt Gly	tgt Cys 95	act Thr	288
tt. Lei	a aat u Asi	t tt 1 Ph	t cci e Pro 100	o Ile	agt Ser	cct Pro	att	gaa Glu 105	Thr	gta Val	cca Pro	gta Val	aaa Lys 110	Lev	aag Lys	336
Pro	a gga o Gly	A ato	t Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	Thr	gaa Glu	gaa Glu	384
aaa Lys	a ata s Ile 130	: Ly:	a gca s Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	Glu	aag Lys	gaa Glu	Gly	432
aaa Lys 145	s Ile	tca Sei	a aaa : Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc	ata Ile	aag Lys	, aaa : Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
agg Arg	gaa Glu	Lev	aat Asn 180	Lys	aaa Lys	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gly aaa	576
ata Ile	cca Pro	cat His 195	Pro	gca Ala	gga Gly	tta Leu	aaa Lys 200	aag Lys	aat Asn	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
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gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	att Ile	tta Leu	gat Asp	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
cag Gln	aat Asn	cca Pro 275	gat Asp	ata Ile	gtt Val	Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864

PCT/US00/30863

-67-

WO 01/35316

gga Gly	tct Ser 290	gac Asp	tta Leu	gag Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	gca Ala	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	gca Ala	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	acc Thr	acc Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
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gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
Ile		gca Ala														1116
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Gly (cag Gln	cta Leu	aag Lys 20	gaa Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	ata Ile	96
tta (Leu (gaa Glu	gac Asp 35	aya Xaa	rat Xaa	ttg Leu	cca Pro	999 Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	ata Ile	ata Ile	ggg Gly	144
gga a Gly :	att Ile 50	gga Gly	ggt Gly	ttt Phe	atc Ile	aga Arg 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	cag Gln	gta Val	ccc Pro	ata Ile	192
gaa a Glu 1 65	atc Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gtt Val	gta Val	agt Ser	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240

-68-

Pr	t gc	c aa a Ası	ata n Ile	a ati e Ile 89	e Gly	aga / Arg	aat JAsr	cto Lev	ato Met 90	Thr	caq Glr	g att	ggt Gly	tgo Cys	act Thr	288	l
tt: Lei	a aat u Asi	t tti n Phe	e Pro) Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	Thr	gta Val	cca Pro	a gta o Val	aaa Lys 110	Lei	a aag 1 Lys	336	1
Pro	a gga o Gly	a ato / Met	: Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	Thr	gaa Glu	gaa Glu	384	
aaa Lys	a ata 5 Ile 130	: Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	Ile	tgt Cys	gaa Glu	gaa Glu	Leu 140	Glu	aag Lys	gat Asp	gly	432	
aaa Lys 145	: Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480	
gcc Ala	ata Ile	aag Lys	aaa Lys	aag Lys 165	aac Asn	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528	
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ata Ile	cca Pro	cat His 195	cct Pro	gca Ala	gga Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624	
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aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720	
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tca Ser	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816	
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtc Val	atc Ile	tat Tyr 280	caa Gln	tat Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864	
gga Gly	tct Ser 290	gac Asp	tta Leu	gag Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912	
aga Arg 305	cag Gln	cat His	ctg Leu	tgg Trp	aag Lys 310	tgg Trp	ggg Gly	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	ara Xaa	aaa Lys	cat His 320	960	

-69-

Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008
aaa tgg aca gta cag cct ata gtg ctg cca gaa aag gac agc tgg act Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350	1056
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
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Pro Gln lie Thr Leu Trp Gln Arg Pro Phe Val Thr Ile Lys Ile Gly	48 96
ggg caa cta aag gaa gct ata tta gac aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Ile Leu Asp Thr Gly Ala Asp Asp Thr Val	
ggg caa cta aag gaa gct ata tta gac aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Ile Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30 tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa atg ata ggg Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly	96
Pro Gln Ile Thr Leu Trp Gln Arg Pro Phe Val Thr Ile Lys Ile Gly 1	96 144
ggg caa cta aag gaa gct ata tta gac aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Ile Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 The Gly Ala Asp Asp Thr Val 20 Arg Trp Lys Pro Lys Met Ile Gly 35 Gly Gly Phe Xaa Lys Val Arg Gln Tyr Asp Gln Val Pro Ile 50 Gaa atc tgt gga cat aaa gtt atg agt aca gta tta ata gga cct aca Gly Ile Gly Gly Phe Xaa Lys Val Arg agt aca gta tta ata gga cct aca Gly Ile Cys Gly His Lys Val Met Ser Thr Val Leu Ile Gly Pro Thr	96 144 192

cca Pro	ggg ggg	atg Met 115	gac Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
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aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
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agt Ser 225	aca Thr	ctg Leu	cat His	tta Leu	cca Pro 230	tac Tyr	cta Leu	gta Val	cgr Xaa	acc Thr 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
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aga Arg 305	caa Gln	cat His	ctg Leu	tgg Trp	aag Lys 310	tgg Trp	ggg Gly	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	cgt Arg	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	caa Gln	gcc Ala	tat Tyr	aaa Lys	gct Ala 345	gcc Ala	aga Arg	aaa Lys	aga Arg	cag Gln 350	ctg Leu	gac Asp	1056

-71-

tgt caa tga cat tac mag aaa gtt agt ggg gaa aat tgg aat ttg ggg Cys Gln * His Tyr Xaa Lys Val Ser Gly Glu Asn Trp Asn Leu Gly 355 360 365	1104
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gga cag cta aag gaa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gaa atg agt ttg cca gga aga tgg aaa cca aaa atg ata ggg Leu Glu Glu Met Ser Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly 35 40 45	144
gga att gga ggt ttt atc aaa gta aga car tat gat cag ata ccm rta Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Xaa Xaa 50 55 60	192
gaa att tgc gga cat aaa gct gta ggt aca gta tta gta gga cct aca Glu Ile Cys Gly His Lys Ala Val Gly Thr Val Leu Val Gly Pro Thr 65 70 75 80	240
cct gtc aac ata att gga aga aat ctg ttg act cag mtt ggt tgc act Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Xaa Gly Cys Thr 85 90 95	288
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-72-

				•												
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ata Ile	cca Pro	cat His 195	cct Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
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cag Gln	aaa Lys	gaa Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	gaa Glu	Leu	His	cct Pro 335	Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	nat Xaa	aca Thr	aaa Lys	gtt Val	agt Ser 360	Gly 999	gaa Glu	aat Asn	tga *	att Ile	999 365	sca Xaa	agt Ser	1104
			tgg Trp		g											1120

-73-

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  <213> Human Immunodificiency Virus (HIV)
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  <221> CDS
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  <223> HIV Protease
  <221> CDS
  <222> (298) ... (1059)
  <223> Portion of HIV Reverse Transcriptase
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Pro Gln Ile Thr Leu Trp Gln Arg Pro Val Val Thr Ile Asn Ile Gly
                                                                                   48
  ggg caa cta aag gaa gct cta tta gac aca gga gca gat gat aca gta
                                                                                   96
 Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val
 tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa atg ata ggg
                                                                                  144
 Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly
 gga att gga ggt ttt atc aaa gta aga cag tat gat cag ata ccc ata
                                                                                  192
 Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Pro Ile
 gaa atc tgt gga cat aaa act ata ggt aca gta tta ata gga cct aca
                                                                                  240
 Glu Ile Cys Gly His Lys Thr Ile Gly Thr Val Leu Ile Gly Pro Thr
 cct gtc aac ata att gga aga aat ctg ttg act cag att ggc tgc act
                                                                                  288
 Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr
 tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag
                                                                                  336
 Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
 cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu
                                                                                  384
 aaa ata aaa gca tta ata gaa att tgt aca gaa atg gaa aag gaa ggg
Lys Ile Lys Ala Leu Ile Glu Ile Cys Thr Glu Met Glu Lys Glu Gly
                                                                                 432
                             135
                                                    140
                                                                                 480
 aaa att tca aaa att ggg cct gaa aac ccg tac aat act cca gtc ttt
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
                        150
 gcc ata aag aaa aaa gat agt act aaa tgg aga aaa tta gta gat ttc
 Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe
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-74-

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ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttc Phe 215	tca Ser	gtt Val	cct Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	aca Thr	aac Asn 235	aat Asn	gag Glu	acg Thr	cca Pro	999 Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gcc Ala	ata Ile	nnn Xaa	nnn Xaa 260	nnn Xaa	nnn Xaa	nnn Xaa	nnn Xaa	nnn Xaa 265	nnn Xaa	nnn Xaa	nnn Xaa	nnn Xaa	nnn Xaa 270	nnn Xaa	nnn Xaa	816
nnn Xaa	nnn Xaa	nnn Xaa 275	nnn Xaa	nnn Xaa	nnn Xaa	nnn Xaa	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	gag Glu 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	aaa Lys	ctg Leu	912
aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	agg Arg 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gat Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttt Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gta Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val																1059

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<220>

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-75-

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ggg Gly	g caa g Glr	a cta 1 Lei	a aag 1 Lys 20	Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	Thr	gta Val	96
tta Leu	gaa Glu	gaa Glu 35	ı Met	g aat : Asn	ttg Leu	cca Pro	gga Gly 40	Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	Met	ata Ile	Gly	144
gga Gly	att Ile 50	: Gly	ggt Gly	ttt Phe	atm Xaa	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	Gln	ata Ile	cyc Xaa	ata Ile	192
gaa Glu 65	Ile	tgt Cys	gga Gly	yat Xaa	aaa Lys 70	gct Ala	ata Ile	ggt Gly	acr Xaa	gta Val 75	tta Leu	gta Val	gga Gly	ccc Pro	acg Thr 80	240
cct Pro	gtc Val	aac Asn	rta Xaa	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	wtg Xaa 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
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aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
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aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aaa Lys	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtc Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	gly aga	tta Leu	aag Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672

-76-

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 1	att Ile	aga Arg	tay Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	caa Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
	gca Ala	ata Ile	tty Phe	caa Gln 260	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aag Lys	816
	caa Gln	aat Asn	cca Pro 275	gac Asp	cta Leu	gtt Val	att Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
	gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
	aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	ara Xaa 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
	cag Gln	aaa Lys	gaa Glu	ccc Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
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	<222)> L> CI 2> ((3> H)))														
	<222	L> CI 2> (2 3> Po	298)	(1 on of	L082) E HIV	/ / Rev	/erse	e Tra	ansci	ripta	ase						
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	Gly 999	caa Gln	cta Leu	aag Lys 20	gaa Glu	gct Ala	yta Xaa	ttr Xaa	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
	tta Leu	gaa Glu	gaa Glu 35	atg Met	aat Asn	tta Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	Gly 999	144

	gga Gly	att Ile 50	gga Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	cag Gln	ata Ile	ccc Pro	ata Ile	192
- -:	gaa Glu 65	aty Xaa	tgt Cys	Gly 999	cat His	aaa Lys 70	gct Ala	ata Ile	ggt Gly	aca Thr	gta Val 75	tta Leu	gta Val	Gly 999	cct Pro	aca Thr 80	240
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	tta Leu	aat Asn	ttt Phe	cct Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
	cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	ccc Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
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	gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
	aaa Lys 225	Tyr	ast Xaa	Ala	ttt Phe	acc Thr 230	Ile	Pro	Ser	Ile	Asn	aat Asn	Glu	aca Thr	cca Pro	999 Gly 240	720
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	gca Ala	ata Ile	ttc Phe	caa Gln 260	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gaa Glu	cct Pro	ttt Phe 270	Arg	aaa Lys	816
	caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864

WO 01/35316 PCT/US00/30863

-78-

ĞÎ	tct Ser 290	Asp	ttg Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 309	cag Gln	cat His	ctg Leu	ttg Leu	aaa Lys 310	tgg Trp	ggr Xaa	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aag Lys	aaa Lys	cat His 320	960
Cag Gl:	g aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	999 Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
	tgg Trp															1056
	aat Asn							99								1082
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	0> 1> Cl 2> (4		. (297	7)				-								
<22	3> H	IV P	rotea	ase												
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<22 <22 <22 <40 cct Pro 1 ggg Gly	1> Cl 2> (2 3> Po 0> 44 cag Gln	OS 298). ortic 1 atc Ile cta Leu	act Thr aag Lys 20	ctt Leu 5 gaa Glu	tgg Trp gct Ala	caa Gln yta Xaa	cga Arg tta Leu	ccc Pro gat Asp 25	atc Ile 10 aca Thr	gtc Val gga Gly	Thr gca Ala cca	Val gat Asp	Lys gat Asp 30 ata	Ile 15 aca Thr	gta Val	
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-11	cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
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	aaa Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	rta Xaa	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
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	cag Gln	aat Asn	cca Pro 275	Asp	ata Ile	Val	atc Ile	Tyr	Gln	Tyr	Val	gat Asp	Asp	Leu	ctt Leu	gta Val	. 864
	gga Gly	tct Ser 290	gat Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	caa Gln	cat His	aga Arg	gca Ala	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
	aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	agg Arg 310	tgg Trp	Gly 999	ttt Phe	atc Ile	aca Thr 315	cca Pro	gac Asp	gaa Glu	aaa Lys	cat His 320	960
	cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008

-80-

Lys Trp Th	a gta cag d r Val Gln 1 340	Pro Ile V a	l Leu Pro	o Glu Lys	Asp Ser	r Trp Thr	1056
gtc aat ga Val Asn As	c ata caa a p Ile Gln I 5	ag tta gt Lys Leu Va 36	l Gly Lys	a ttg aat s Leu Asr	tgg gca Trp Ala 365	a agc cag a Ser Gln	1104
att tat go Ile Tyr Al 370						·	1116
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)(1116) ion of HIV	Reverse Ti	ranscript	ase			
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ggg cag cta Gly Gln Lev	a aag gaa g 1 Lys Glu A 20	ct cta tta la Leu Leu	gat aca Asp Thr 25	gga gca Gly Ala	gac gat Asp Asp 30	aca gta Thr Val	96
tta gaa gaa Leu Glu Glu 35	Met Asn L	ta cca gga eu Pro Gly 40	Lys Trp	aaa cca Lys Pro	aaa atg Lys Met 45	ata gtg Ile Val	144
gga att gga Gly Ile Gly 50	gga ttt g Gly Phe Va	c aaa gta al Lys Val 55	aaa cag Lys Gln	tat gag Tyr Glu 60	caa ata Gln Ile	cct gta Pro Val	192
gaa atc tgt Glu Ile Cys 65	Gly His Ly	aa gct gta vs Ala Val 70	ggt aca Gly Thr	gta tta Val Leu 75	gta gga Val Gly	cct aca Pro Thr 80	240
cct gcc aac Pro Ala Asn	ata att gg Ile Ile Gl 85	ga aga aat .y Arg Asn	ctg ttg Leu Leu 90	act cag Thr Gln	att ggt Ile Gly	tgc act Cys Thr 95	288
tta aat ttt Leu Asn Phe	CCC att ac Pro Ile Se 100	t cct att r Pro Ile	gaa act Glu Thr 105	gta cca Val Pro	gta aaa Val Lys 110	tta aag Leu Lys	336
cca gga atg Pro Gly Met 115	gat ggc co Asp Gly Pr	a aaa gtt o Lys Val 120	aaa caa Lys Gln	tgg cca Trp Pro	ttg aca Leu Thr 125	aaa gar Lys Glu	384

-81-

		maa Xaa					Ile									432
	: Ile	tca Ser														480
		aag Lys														528
		ctt Leu														576
		cat His 195														624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	rtt Xaa	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gaa Glu	ttc Phe	agg Arg	672
	Tyr	act														720
		tat Tyr														768
		ttc Phe					Thr									816
		cca Pro 275														864
		gac Asp														912
		cat His														960
		gaa Glu													Asp	1008
		act Thr														1056
gtc Val	aat Asn	gac Asp 355	cta Leu	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104

-82-

370	
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ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gaa atg aat ttg cca gga agg tgg aaa cca aaa atg ata ggg Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly 35 40 45	144
gga att gga ggt ttt atc aaa gta aga cag tat gat cag ata tcc ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Ser Ile 50 55 60	192
gaa atc tgt gga cat aaa gct ata ggt aca gta tta gta gga cct aca Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr 65 70 75 80	240
cct gtc aac ata att gga aga aat ctg ttg act cag att ggt tgc act Pro Val Asn_Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr 85 90 95	288
tta aat ttt cct att agt cct att gaa act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336
cca gga atg gac ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta gta gag att tgt aca gaa atg gaa aag gaa gga Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly 130 135 140	432
aaa att tca aaa att ggg cct gaa aac cca tac aat act cca gta ttt Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe 145 150 155 160	480

-83-

gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aag Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
					aga Arg											576
					ggg Gly											624
					tat Tyr											672
					acc Thr 230											720
act Thr	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctc Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
					agc Ser											816
					gtt Val											864
					ata Ile											912
					agg Arg 310											960
					ttt Phe											1008
					cct Pro	Ile	Val	Leu								1056
					aag Lys	Leu										1104
att Ile		cca Pro														1116

<210> 47 <211> 1116 -84-

	12> I 13> I		ı Imn	nunod	lific	ienc	y Vi	rus	(HIV	7)						
<22	20> 21> 0 22> (23> H	(0)														
<22 <22		(298) Porti				vers	e Tr	ansc	ript	ase						
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				Glu				gat Asp 25						Thr	gta Val	96
			Met					aga Arg								144
gga Gly	att Ile 50	Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	caa Gln	tat Tyr	gat Asp 60	cag Gln	gta Val	gcc Ala	atg Met	192
	Ile							ggt Gly								240
cct Pro	gtc Val	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr	288
								gaa Glu 105								336
cca Pro	ggr Xaa	atg Met 115	gat Asp	ggt Gly	cca Pro	agg Arg	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	Xaa	Ala	Leu	Val	Glu	Ile	tgt Cys	Thr	Glu	Met	gaa Glu	aag Lys	gaa Glu	gga Gly	432
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttt Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aaa Lys	act Thr	caa Gln	gac Asp 185	tty Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	ggr Xaa	576

-85-

ata Ile	ccg Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctt Leu	624
gat Asp	gtg Val 210	gga Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gat Asp	ttc Phe	agg Arg	672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
att Ile	aga Arg	tat Tyr	caa Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	att Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aag Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	gga Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctr Xaa	912
aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	gly aaa	ytt Xaa	acc Thr	aca Thr 315	cca Pro	gac Asp	aag Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	ccy Xaa	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggk Xaa 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aar Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
	tat Tyr 370															1116
<211 <212)> 48 L> 11 !> DN	.15 IA	Immu	ınodi	.fici	ency	v Vir	rus ((HIV)							

<213> Human Immunodificiency Virus (HIV)

<220>

<221> CDS <222> (0)...(297) <223> HIV Protease

-86-

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-87-

aag tat act gca ttt acc ata cct agt ata aac aat gag aca cca ggg Lys Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly 225 230 235 240	720
att aga tat cag tac aat gtg ctk cca cag gga tgg aag gga tca cca Ile Arg Tyr Gln Tyr Asn Val Xaa Pro Gln Gly Trp Lys Gly Ser Pro 245 250 255	768
gca ata ttc caa agt agc atg aca aaa atc ttg gag ccc ttt aga aaa Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys 260 265 270	816
caa aat cca gac cta gtt atc tat caa tac atg gat gat ttg tat gta Gln Asn Pro Asp Leu Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val 275 280 285	864
ggc tct gac tta gaa ata ggg cag cat aga aca aaa ata gag gaa ctg Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu 290 295 300	912
aga caa cat ctg ttg aag tgg gga ttt acc aca cca gat aaa aaa cat Arg Gln His Leu Leu Lys Trp Gly Phe Thr Thr Pro Asp Lys Lys His 305 310 315 320	960
cag aaa gaa cct cca ttt ctt tgg atg ggt tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008
aaa tgg aca gta cag cct ata gtg ctg cca gaa aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350	1056
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
att tcc car ga Ile Ser Gln 370	1115
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-88-

Gl ³ aaa	g cag Glr	j cta Lev	a aag Lys 20	Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	Thr	gta Val	96
tta Leu	gaa Glu	gaa Glu 35	. Met	aat Asn	ttg Leu	cca Pro	gga Gly 40	Arg	tgg Trp	aaa Lys	cca Pro	aag Lys 45	Met	ata Ile	Gly 999	144
		Gly										Gln		ccc Pro		192
	Ile										Leu			cct Pro		240
														tgc Cys 95		288
														tta Leu		336
														gaa Glu		384
														gaa Glu		432
														gta Val		480
														gat Asp 175		528
														tta Leu		576
														gta Val		624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gaa Glu	ttc Phe	agg Arg	672
														cca Pro		720
atc Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768

-89-

														Arg	aaa Lys	816
	aat Asn							Gln							gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	gta Val	gag Glu	gag Glu	ctg Leu	912
	caa Gln															960
	aaa Lys															1008
	tgg Trp															1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	aat Asn	tgg Trp 365	gca Ala	agc Ser	cag Gln	1104
	tac Tyr 370															1116
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<222)> !> CI !> (0 !> HI)														
<222	> CD > (2 > Po	98).			Rev	erse	Tra	nscr	ipta	.se						
cct	> 50 cag Gln	atc : Ile '	act Thr	ctt Leu 5	tgg Trp	caa Gln	cga Arg	ccc Pro	ttc Phe 10	gtc Val	aac Asn	ata Ile	aag Lys	ata Ile 15	ggg Gly	48
gga Gly	caa Gln	ctg : Leu :	aag (Lys (20	gaa Glu	gct Ala	cta Leu	ttg Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
	gaa (Glu (144

-90-

gga Gly	att Ile 50	gga Gly	ggt Gly	ttk Xaa	gtc Val	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	cag Gln	ata Ile	cct Pro	gta Val	192
gaa Glu 65	att Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gyt Xaa	ata Ile	ggt Gly	aca Thr	gtc Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
cct Pro	gcc Ala	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggc Gly	tgc Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	ccg Pro	aga Arg	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	ttg Leu 140	gaa Glu	aag Lys	gaa Glu	gga Gly	432
aaa Lys 145	att Ile	tca Ser	aag Lys	att Ile	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	ata Ile	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aag Lys 165	aac Asn	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	gly aaa	tta Leu	mam Xaa 200	aag Lys	aac Asn	aaa Lys	tca Ser	gta Val 205	aca Thr	gtg Val	cta Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	tat Tyr 220	gaa Glu	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	tat Tyr	act Thr	gca Ala	Phe	acc Thr 230	Ile	Pro	agt Ser	Thr	Asn	Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tay Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	cag Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aga Arg 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
	aat Asn															864

WO 01/35316 PCT/US00/30863

-91-

Ala Ser Asp Leu Glu Ile Glu Lys His Arg Thr Lys Ile Glu Glu Leu 290 295 300	912
aga caa cat ctg ttg agg tgg gga ttt tac aca cca gac aaa aag cat Arg Gln His Leu Leu Arg Trp Gly Phe Tyr Thr Pro Asp Lys Lys His -305 310 315 320	960
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008
aaa tgg aca gta cag cct ata gtg ctg cca gaa aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350	1056
gtc aat gac ata cag aaa tta gtg gga aaa ttg aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
att tat gga ggg Ile Tyr Gly Gly 370	1116
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<pre><223> HIV Protease <221> CDS <222> (298)(1116) <223> Portion of HIV Reverse Transcriptase <400> 51 cct cag atc act ctt tgg caa cga ccc atc gtc aca ata aag ata ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile Gly 1</pre>	
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	cct Pro	gcc Ala	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	gat Asp	ctg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr		288
_	tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	ttg Leu	aag Lys		336
	cca Pro	gga Gly	atg Met 115	gat Asp	ggt Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu		384
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	ata Ile	cca Pro	cat His 195	ccc Pro	gcg Ala	gly aaa	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	-	624
	gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	att Ile	ccc Pro	tta Leu	gat Asp 220	gaa Glu	gaa Glu	ttc Phe	agg Arg	•	672
	aag Lys 225	tat Tyr	act Thr	gca Ala	ttc Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240		720
	gtt Val	aga Arg	tat Tyr	caa Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro		768
	gca Ala	ata Ile	Phe	caa Gln 260	Ser	Ser	Met	Thr	Lys	Ile	tta Leu	Glu	Pro	Phe	Arg	aaa Lys		816
	caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tat Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val		864
	gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	gca Ala	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu		912
	aga Arg 305	caa Gln	cat His	ctg Leu	tgg Trp	agg Arg 310	tgg Trp	gly aga	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320		960

WO 01/35316 PCT/US00/30863

-93-

GII	aaa Lys															1008
	tgg Trp															1056
	aat Asn															1104
	tat Tyr 370											,				1116
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<22	0 > 1 > Cl 2 > (0 3 > Hi	0)														
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	0 > 5	2					•									
	Gln													rta Xaa 15		48
Pro 1 999		Ile	Thr	Leu 5 gaa	Trp	Gln	Arg	Pro gat	Leu 10 aca	Val gga	Thr	Ile gat	Lys gat	Xaa 15 aca	Gly	96
Pro 1 999 Gly	Gln	Ile cta Leu gaa	Thr aag Lys 20 atg	Leu 5 gaa Glu aat	Trp gct Ala ttg	Gln cta Leu cca	Arg tta Leu gga	Pro gat Asp 25 aga	Leu 10 aca Thr	Val gga Gly aaa	Thr gca Ala cca	Ile gat Asp	Lys gat Asp 30	Xaa 15 aca Thr	gta Val	
Pro 1 999 Gly tta Leu	Gln caa Gln gaa	Ile cta Leu gaa Glu 35	Thr aag Lys 20 atg Met	Leu 5 gaa Glu aat Asn	Trp gct Ala ttg Leu	Gln cta Leu cca Pro	Arg tta Leu gga Gly 40 gta	gat Asp 25 aga Arg	Leu 10 aca Thr tgg Trp	Val gga Gly aaa Lys	Thr gca Ala cca Pro	gat Asp aaa Lys 45	gat Asp 30 atr Xaa	Xaa 15 aca Thr ata Ile	Gly gta Val ggg Gly	96
Pro 1 999 Gly tta Leu 99a Gly	Caa Gln gaa Glu att Ile	Cta Leu gaa Glu 35 gga Gly	Thr aag Lys 20 atg Met ggt Gly	Leu 5 gaa Glu aat Asn ttt Phe	gct Ala ttg Leu atc Ile aaa	Cta Leu Cca Pro aaa Lys 55	tta Leu gga Gly 40 gta Val	gat Asp 25 aga Arg aga Arg	Leu 10 aca Thr tgg Trp cag Gln tca	Val gga Gly aaa Lys tat Tyr	Thr gca Ala cca Pro gat Asp 60 tta	gat Asp aaa Lys 45 cag Gln	gat Asp 30 atr Xaa ata Ile	Xaa 15 aca Thr ata Ile ycc Xaa	Gly gta Val ggg Gly ata Ile	96 144
ggg Gly tta Leu gga Gly gaa Glu 65 cct	caa Gln gaa Glu att Ile 50 atc	cta Leu gaa Glu 35 gga Gly tgt Cys	Thr aag Lys 20 atg Met ggt Gly gga Gly ata	Leu 5 gaa Glu aat Asn ttt Phe cat His	Trp gct Ala ttg Leu atc Ile aaa Lys 70 gga	Cta Leu Cca Pro aaa Lys 55 gct Ala	tta Leu gga Gly 40 gta Val ata Ile	gat Asp 25 aga Arg aga Arg	Leu 10 aca Thr tgg Trp cag Gln tca Ser	gga Gly aaa Lys tat Tyr gta Val 75 act	Thr gca Ala cca Pro gat Asp 60 tta Leu cag	gat Asp aaa Lys 45 cag Gln gta Val	Lys gat Asp 30 atr Xaa ata Ile gga Gly	Xaa 15 aca Thr ata Ile ycc Xaa cct Pro	Gly gta Val ggg Gly ata Ile aca Thr 80 act	96 144 192

cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aag Lys	caa Gln	tgg Trp	cca Pro	Leu 125	aca Thr	gra Xaa	gaa Glu		384
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gca Ala	ata Ile	ttc Phe	caa Gln 260	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys 265	aty Xaa	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys		816
car Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val		864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	gaa Glu 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ttg Leu		912
aga Arg 305	caa Gln	cat His	ctg Leu	tta Leu	agg Arg 310	tgg Trp	gga Gly	ttt Phe	ttc Phe	aca Thr 315	cca Pro	gaa Glu	caa Gln	aaa Lys	cat His 320		960
cag Gln	aaa Lys	gaa Glu	ccg Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	cta Leu	cat His	cct Pro 335	gat Asp	1	.008
aaa Lys	tgg Trp	acg Thr	gta Val 340	cag Gln	cct Pro	ata Ile	aag Lys	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gat Asp	agc Ser 350	tgg Trp	act Thr	1	.056

-95-

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ggg caa cta aaa gaa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96													
tta gaa gaa atg aat tta cca gga aga tgg aaa cca aaa atg ata ggg Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly 35 40 45	144													
gga att gga ggt ttt atc aaa gtg aga cag tat gat cag rta ccc ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Xaa Pro Ile 50 55 60	192													
gaa att tgt gga cat aaa gct ata ggt aca gta tta gta gga tct aca Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Ser Thr 65 70 75 80	240													
cct gtc aac ata att gga aga aat ctg ttg act cag ctt ggg tgc act Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Leu Gly Cys Thr 85 90 95	288													
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336													
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384													
aaa ata aaa gca tta gta gaa att tgt aca gag atg gaa aag gaa ggg Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly 130 135 140	432													

-96-

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	aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aaa Lys	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
	atc Ile	cca Pro	cat His 195	cct Pro	gca Ala	Gly ggg	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
	gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	cgg Arg	672
	aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	aca Thr	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	gga Gly 240	720
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	gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	agg Arg	aat Asn	816
	aaa Lys	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
	gga Gly	tct Ser 290	gac Asp	cta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	gca Ala	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
	aga Arg 305	gaa Glu	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	ggg ggg	ttt Phe	act Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
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	gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
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PCT/US00/30863 WO 01/35316

-97-

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  <223> HIV Protease
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                                                                                96
  ggg caa cta aag gaa gct yta tta gat aca gga gca gat gat aca gta
  Gly Gln Leu Lys Glu Ala Xaa Leu Asp Thr Gly Ala Asp Asp Thr Val
                                                                               144
  tta gaa gac atg gat ttg cca gga aga tgg aaa cca aaa atg ata gtg
  Leu Glu Asp Met Asp Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Val
  gga att gga ggt ttt gtc aaa gta aga cag tat gat cag ata ccc ata
                                                                              192
  Gly Ile Gly Gly Phe Val Lys Val Arg Gln Tyr Asp Gln Ile Pro Ile
  gaa atc tgt gga cat aaa att ata ggt aca gta tta ata gga aat aca
                                                                               240
  Glu Ile Cys Gly His Lys Ile Ile Gly Thr Val Leu Ile Gly Asn Thr
  cct gcc aac gta att gga aga aat ctg ttg act cag ctt ggt tgc act
                                                                              288
  Pro Ala Asn Val Ile Gly Arg Asn Leu Leu Thr Gln Leu Gly Cys Thr
                                                                              336
  tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag
  Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
  cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa
                                                                              384
  Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu
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  aaa ata aaa gca tta gta gaa att tgt aca gaa ctg gaa aag gat ggg
  Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Asp Gly
                            135
      130
                                                                              480
  aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt
  Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
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 gcc ata aag aaa aag gac agt act aaa tgg aga aaa gta gta gat ttc Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Val Val Asp Phe
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-98-

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								gtt Val								672
								agt Ser								720
								cca Pro								768
								aaa Lys 265								816
								caa Gln								864
								cac His								912
								ttt Phe								960
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-99-

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-100-

gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aag gac ttc agg Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Asp Phe Arg 210 215 220	672											
aag tat act gca ttt acc ata cct agt gta aac aat gag aca cca ggg Lys Tyr Thr Ala Phe Thr Ile Pro Ser Val Asn Asn Glu Thr Pro Gly 230 235 240	720											
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gca ata ttt caa agt agc atg aca aaa atc tta gag cct ttt aga aaa Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys 260 265 270	816											
caa aat cca gac atg gtt atc tat caa tac atg gat gat ttg tat gta Gln Asn Pro Asp Met Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val 275 280 285	864											
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agg cag cat ctg ttg agg tgg gga ttt acc aca cca gac aaa aag cat Arg Gln His Leu Leu Arg Trp Gly Phe Thr Thr Pro Asp Lys Lys His 305 310 315 320	960 [.]											
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008											
aaa tgg aca gta cag cct ata ktg ctg cca gaa aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Xaa Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350	1056											
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att tam ccc ngg Ile Xaa Pro Xaa 370	1116											
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-101-

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						aaa Lys 70											240
						gga Gly											288
						agt Ser											336
						cca Pro											. 384
						gta Val											432
						999 Gly 150											480
						gat Asp											528
				Asn	Lys	aga Arg	Thr	Gln	Āsp	Phe	Trp	Glu	Val				576
						gly ggg											624
	gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gaa Glu	ttc Phe	agg Arg	672
	aag Lys 225	tat Tyr	act Thr	gca Ala	ttc Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720

-102-

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14	gca Ala	ata Ile	ttc Phe	caa Gln 260	agc Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	att Ile	tta Leu	gaa Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
	caa Gln	aat Asn	cca Pro 275	gaa Glu	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
	gga Gly	tct Ser 290	gac Asp	tta Leu	raa Xaa	ata Ile	gag Glu 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
	aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	agg Arg 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aag Lys	cat His 320	960
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	gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
			cca Pro														1116
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-103-

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gat Asp	gtg Val 210	Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	cca Pro	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	aca Thr	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	caa Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cca Pro	ttt Phe 270	aga Arg	aaa Lys	816

-104-

caa aat cca gac ata gtt atc tgt caa tac atg gat gat ttg tat gta Gln Asn Pro Asp Ile Val Ile Cys Gln Tyr Met Asp Asp Leu Tyr Val 275 280 285	864
gga tct gac tta gaa ata gag cag cat aga aca aaa ata gag gaa ctg Gly Ser Asp Leu Glu Ile Glu Gln His Arg Thr Lys Ile Glu Glu Leu 290 295 300	912
aga caa cat ctg ttg agg tgg gga ttt tac aca cca gac caa aaa cat Arg Gln His Leu Leu Arg Trp Gly Phe Tyr Thr Pro Asp Gln Lys His 305 310 315 320	960
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008
aaa tgg aca gta cag cct ata acg ctg cca gac aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Thr Leu Pro Asp Lys Asp Ser Trp Thr 340 345 350	1056
gtc aat gac ata cag aag tta gtg gga aaa tta aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
att tat gca ggg Ile Tyr Ala Gly 370	1116
<210> 58 <211> 1116 <212> DNA <213> Human Immunodificiency Virus (HIV)	
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ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gaa atg act ttg cca gga aaa tgg aaa cca aaa atg ata ggg Leu Glu Glu Met Thr Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly 35 40 45	144
gga att gga ggt ttt atc aaa gta aga car tat gat cag ata ctc ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Leu Ile 50 55 60	192

-105-

	u Ile					Ala					. Leu				aca Thr 80		240
					Gly					Thr					act Thr		288
tta Le:	a aat 1 Asr	ttt Phe	Pro 100	Ile	agt Ser	cct Pro	att	gag Glu 105	Thr	gta Val	cca Pro	gta Val	aaa Lys 110	Leu	aag Lys		336
Pro	a gga o Gly	atg Met	Asp	ggc	cca Pro	aga Arg	gtt Val 120	. Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	Thr	gaa Glu	gaa Glu		384
		Lys					Ile								gl ^A aaa	•	432
aaa Lys 145	Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160		480
									tgg Trp 170							<u>:</u>	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly		576
ata Ile	cca Pro	cat His 195	cca Pro	gca Ala	Gly Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	E	524
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg		572
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	7	720
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gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	ata Ile 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	8	316
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	8	64
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	Ile	999 Gly 295	cag Gln	cat His	aga Arg	Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	9	12

WO 01/35316 PCT/US00/30863

-106-

aga cag cat ctg ttg agg tgg gga ttt acc aca cca gac aaa aaa cat Arg Gln His Leu Leu Arg Trp Gly Phe Thr Thr Pro Asp Lys Lys His 305 310 315 320	960
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cca gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008
aaa tgg aca gta cag cct ata aag ctg cca gac aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Lys Leu Pro Asp Lys Asp Ser Trp Thr 340 345 350	1056
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
att tat gca gga Ile Tyr Ala Gly 370	1116
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ggg caa cta aaa gaa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
	3.4.4
tta gaa gaa ata aat ttg cca ggg aaa tgg aaa cca maa atg ata ggg Leu Glu Glu Ile Asn Leu Pro Gly Lys Trp Lys Pro Xaa Met Ile Gly 35 40 45	144
Leu Glu Glu Ile Asn Leu Pro Gly Lys Trp Lys Pro Xaa Met Ile Gly	192
Leu Glu Glu Ile Asn Leu Pro Gly Lys Trp Lys Pro Xaa Met Ile Gly 35 40 45 gga att gga ggt ttt att aaa gta aga cag tat gat caa ata gcc ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Ala Ile	

-107-

	tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
-4	cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
	aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	rta Xaa	gaa Glu 135	atc Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	Gly ggg	432
	aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
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	aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtc Val	caa Gln 190	tta Leu	gga Gly	576
	ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	gly ggg	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	cta Leu	624
	gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttc Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gac Asp 220	caa Gln	gac Asp	ttc Phe	agg Arg	672
	aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
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	gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	gta Val	gag Glu	gaa Glu	ctg Leu	912
	aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	agr Xaa 310	tgg Trp	gly ggg	ttt Phe	tmc Xaa	acg Thr 315	cca Pro	gac Asp	aaa Lys	aag Lys	cat His 320	960
	cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008

WO 01/35316 PCT/US00/30863

-108-

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gtc a Val A	aat ga Asn As 35	p Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
Ile T	ac co Tyr Pr 370														1116
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	CDS (298 Port	-	_ `		vers	e Tra	ansci	ripta	ase						
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ggg c	aa ct In Le	a aaa u Lys 20	gaa Glu	gct Ala	cta Leu	tta Leu	gay Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
	aa ga lu Gl 3	u Met													144
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gaa a Glu I 65	tt tg le Cy	t gga s Gly	cat His	aaa Lys 70	gct Ala	ata Ile	ggt Gly	aca Thr	gta Val 75	tta Leu	ata Ile	gga Gly	cct Pro	aca Thr 80	240
cct g Pro V	tc aadal Asi	c ata n Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	atg Met 90	act Thr	cag Gln	ctt Leu	ggc Gly	tgc Cys 95	act Thr	288
tta a Leu A	at tti sn Ph	cct Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca g Pro G	ga atq ly Med 11	: Asp	ggc Gly	cca Pro	aga Arg	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gag Glu	384

This page is not part of the pamphlet!

WO 01-35316 4/5

Date: 17 may 2001

Destination: Agent

Address:

-109-

aaa Lys	ata Ile 130	. Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	Glu	aag Lys	gaa Glu	gga Gly	432
	Ile					Pro					Asn				ttt Phe 160	480
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		act Thr														720
		tat Tyr														768
		tty Phe														816
		cca Pro 275														864
gca Ala	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	gag Glu 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
		cat His														960
		gaa Glu														1008
		aca Thr														1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104

-110-

			gca Ala														1110
_	<21 <21	_	.116 NA	Imm	unod	lific	ienc	y Vi	rus	(HIV	·)						
	<22	1> C 2> (DS 0)														
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	cct		atc						ccc Pro							agg Arg	4.8
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									aga Arg								192
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									gaa Glu 105								336
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									aat Asn								480

-111-

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	cca Pro															624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gaa Glu	agc Ser	ttc Phe	agg Arg	672
	tac Tyr															720
rca Xaa	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gaa Glu	atg Met	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gag Glu	ata Ile	gag Glu 295	caa Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	agg Arg 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
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aaa Lys	tgg Trp	Thr	gta Val 340	cag Gln	cct Pro	ata Ile	Val	ctg Leu 345	cca Pro	gaa Glu	aag Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
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ggg cag c Gly Gln L				p Thr						96
tta gaa ga Leu Glu G										144
gga att gg Gly Ile Gl 50	ga ggt tt .y Gly Pho	t atc aaa e Ile Lys 55	Val Ar	a caa g Gln	Tyr As	at cag sp Gln 50	ata Ile	gcc Ala	ata Ile	192
gaa atc to Glu Ile Cy 65	nt gga car rs Gly His	aaa gct Lys Ala 70	ata ggi lle Gly	t aca y Thr	gta tt Val Le 75	a ata u Ile	gga Gly	cct Pro	aca Thr 80	240
cct gtc aa Pro Val As	c ata ati n Ile Ile 89	e Gly Arg	aat cto Asn Le	atg 1 Met 90	act ca Thr Gl	g att n Ile	ggc Gly	tgc Cys 95	act Thr	288
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cca gga at Pro Gly Me 11	t Asp Gly	cca aaa Pro Lys	gtt aaa Val Lys 120	caa Gln	tgg cc Trp Pr	a ttg o Leu 125	aca Thr	gaa Glu	gaa Glu	384
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aaa att tc Lys Ile Se 145	a aaa att r Lys Ile	ggg cct Gly Pro 150	gaa aat Glu Asn	Pro	tac aa Tyr As 155	t act n Thr	cca Pro	gta Val	ttt Phe 160	480
gcc ata aa Ala Ile Ly	g aaa aag s Lys Lys 165	Asn Ser	act aaa Thr Lys	tgg Trp 170	aga aa Arg Ly	a tta s Leu	Val	gat Asp 175	ttc Phe	528
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-113-

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aag Lys 225	Tyr	act	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
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gca Ala	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	gag Glu 295	cag Gln	cat His	aga Arg	ata Ile	aaa Lys 300	ata Ile	gag Glu	gaa Glu	cta Leu	912
aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	yat Xaa 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gar Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
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-114-

<221> CDS <222> (298) . . . (1116) <223> Portion of HIV Reverse-Transcriptase eet caa ate act ett tgg caa ega eee gtt gtt aca gta agg ata ggg 48 Pro Gln Ile Thr Leu Trp Gln Arg Pro Val Val Thr Val Arg Ile Gly gga cag cta acg gaa gct yta tta gat aca gga gca gat gat aca gta Gly Gln Leu Thr Glu Ala Xaa Leu Asp Thr Gly Ala Asp Asp Thr Val 96 tta gaa gaa atg act ttg cca gga aaa tgg aaa cca aaa ata ata ggg 144 Leu Glu Glu Met Thr Leu Pro Gly Lys Trp Lys Pro Lys Ile Ile Gly ggr att gga ggt ttt atc aaa gta aga cag tat gat cac gta ctt gta 192 Xaa Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp His Val Leu Val gaa atc tgt gga cat aaa gct ata ggt aca gta tta ata gga cct aca 240 Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Ile Gly Pro Thr cct gtc aac ata att gga aga aat ttg atg act cag ctt ggg ttc act 288 Pro Val Asn Ile Ile Gly Arg Asn Leu Met Thr Gln Leu Gly Phe Thr tta aat ttt cca att agt cct att gaa act gta cca gta aaa tta aag 336 Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 cca ggg atg gat ggc cca aaa gtt aaa caa tgg cca ttg mca gaa gaa 384 Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Xaa Glu Glu aaa ata aaa gca cta aca gaa att tgt aca gaa ttg gaa aag gaa gga Lys Ile Lys Ala Leu Thr Glu Ile Cys Thr Glu Leu Glu Lys Glu Gly 432 aaa att tca aga ata ggg cct gaa aat cca tac aat act cca ata ttt Lys Ile Ser Arg Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Ile Phe 480 155 gcc ata aag aag aaa aac ggt ayt agg tgg aga aaa tta gta gat ttc 528 Ala Ile Lys Lys Lys Asn Gly Xaa Arg Trp Arg Lys Leu Val Asp Phe 165 aga gag cta aat aag aga act caa gac ttc tgg gaa gtt caa cta gga 576 Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly 190 ata cca cat cct gca gga cta aaa aag aac aaa tca gta aca gta ctg 624 Ile Pro His Pro Ala Gly Leu Lys Lys Asn Lys Ser Val Thr Val Leu gat gtg ggt gat gca tat ttt tca gtt ccc tta cat gaa gac ttt aga Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu His Glu Asp Phe Arg 672 215

-115-

aag Lys 225	: Tyr	acc Thr	gca Ala	ttc Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	aca Thr	aac Asn 235	aat Asn	gaa Glu	aca Thr	cca Pro	gga Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	caa Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	ccg Pro	768
gca	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	acc Thr	aaa Lys 265	atc Ile	tta Leu	gaa Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gaa Glu	atg Met	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	ata Ile	aaa Lys 300	ata Ile	gag Glu	gaa Glu	tta Leu	912
agg Arg 305	gaa Glu	cac His	cta Leu	ttg Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	ttc Phe	acc Thr 315	cca Pro	gac Asp	gaa Glu	aag Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttt Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctt Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gtg Val 340	cag Gln	cct Pro	ata Ile	aaa Lys	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gaa Glu	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gat Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	aat Asn	tgg Trp 365	gca Ala	agc Ser	cag Gln	1104
		cca Pro								•						1116
<211 <212)> 64 .> 11 !> DN !> Hu	16	Immu	nodi	fici	ency	Vir	us (HIV)							
<222	> CD > (0	S) V Pr														
<222		S 98). rtio				erse	Trai	nscr	ipta	se						
cct	> 64 cag Gln	atc a Ile :	act o	ctt (Leu : 5	tgg (Irp (caa (Gln)	cga (Arg)	ecc (Pro :	atc (Ile 1	gtc . Val '	aca a	ata Ile	aag Lys	ata (Ile (gly 999	48

-116-

				Glu										Thr	gta Val	96
tta Leu	gaa Glu	gaa Glu 35	Met	aat Asn	tta Leu	cca Pro	gga Gly 40	Lys	tgg Trp	aaa Lys	. cca Pro	aaa Lys 45	Xaa	ata Ile	Gly	144
gga Gly	att Ile 50	Gly	99y Xaa	ttt Phe	rtc Xaa	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	Gln	ata Ile	syc Xaa	ata Ile	192
	Ile				aaa Lys 70						Leu					240
					gga Gly											288
					agt Ser											336
					cca Pro											384
					gta Val											432
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gct Ala	ata Ile	aag Lys	aaa Lys	aag Lys 165	gac Asp	agt. Ser	gct Ala	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
					aga Arg											576
					gly ggg											624
gat Asp	gta Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	caa Gln	aac Asn	ttc Phe	aga Arg	672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttc Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	ayg Xaa	cca Pro	999 Gly 240	720
att Ile	aga Arg	tat Tyr	Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768

WO 01/35316 PCT/US00/30863

-117-

gca ata ttc caa agt agc atg aca aaa atc tta gag cct ttt aga aaa Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys 260 265 270	816
caa aat cca gar ata rtt atc tat caa tac gtg gat gat ttg tat gta Gln Asn Pro Glu Ile Xaa Ile Tyr Gln Tyr Val Asp Asp Leu Tyr Val 275 280 285	864
gga tct gac ttr gaa ata ggg cag cat aga aca aaa ata gag gaa ctg Gly Ser Asp Xaa Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu 290 295 300	912
aga caa cat ytg ttg aag tgg gga ttt acc aca cca gac aag aag cat Arg Gln His Xaa Leu Lys Trp Gly Phe Thr Thr Pro Asp Lys Lys His 305 310 315 320	960
cag aaa gaa cct cca ttc ctt tgg atg ggg tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008
aaa tgg aca gta cag cct ata atg ctg cca gaa aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Met Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350	1056
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
att tat gca gga Ile Tyr Ala Gly 370	1116
<210> 65 <211> 1116 <212> DNA <213> Human Immunodificiency Virus (HIV)	
<220> <221> CDS <222> (0)(297) <223> HIV Protease	
<221> CDS <222> (298)(1116) <223> Portion of HIV Reverse Transcriptase	
<pre><400> 65 cct cag atc act ctt tgg caa cga ccc atc gtc aca ata aag ata ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile Gly 1 5 10 15</pre>	48
ggg cag cta aag gaa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gac atc aat ttg cca gga aaa tgg aaa cca aaa atg ata ggg Leu Glu Asp Ile Asn Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly 35 40 45	144

-118-

		Gly													ata Ile	192
	Ile		gga Gly													240
			ata Ile		ĞĬy											288
			ccc Pro 100													336
			gat Asp													384
			gca Ala													432
			aaa Lys													480
			aaa Lys													528 [.]
			aat Asn 180													576
			ccc Pro													624
			gat Asp													672
Lys		Thr	gca Ala	Phe	Thr	Ile	Pro	Ser	Ile	Asn	Asn					720
			cag Gln													768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	att Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
			gac Asp			Ile										864

-119-

gga tct gat ttg gaa ata gag cag cat aga aca aaa ata gag gaa cta Gly Ser Asp Leu Glu Ile Glu Gln His Arg Thr Lys Ile Glu Glu Leu 290 295 300	912
aga gaa cat ctg tgg aag tgg gga ttt tac aca cca gac aaa aaa cat Arg Glu His Leu Trp Lys Trp Gly Phe Tyr Thr Pro Asp Lys Lys His 305 310 315 320	960
cag aag gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008
aaa tgg aca gta cag cct ata aag ytg cca gaa aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Lys Xaa Pro Glu Lys Asp Ser Trp Thr 340 345 350	1056
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt caa Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
att tat cca ggg Ile Tyr Pro Gly 370	1116
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ggg caa cta aag gaa gct cta tta gat aca gga gca gat gak rca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Xaa Xaa Val 20 25 30	96
tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa atg ata ggg Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly 35 40 45	144
gga att gga ggt ttt atc aaa gta agr car tat gac cag ata ccc ata Gly Ile Gly Gly Phe Ile Lys Val Xaa Gln Tyr Asp Gln Ile Pro Ile 50 55 60	192
gaa atc tgt gga cag aaa gct ata ggt aca gta tta gta gga cct acm Glu Ile Cys Gly Gln Lys Ala Ile Gly Thr Val Leu Val Gly Pro Xaa 65 70 80	240

-120-

					Gly										act Thr	28
				Ile											aag Lys	33
			Asp					Lys							gaa Glu	38
		Lys													gga Gly	43
						cct Pro										48
						agt Ser										52
						act Thr										57
				_		tta Leu		_				_				62
						ttt Phe 215										67
						ata Ile										72
						gtg Val										768
_				_	_	ayg Xaa								_		816
						atc Ile										864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ttg Leu	912
						tgg Trp										960

WO 01/35316 PCT/US00/30863

-121-

Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro	
aaa tgg aca gta cag cct ata aaa ctg cca gaa aaa gay agc tgg Lys Trp Thr Val Gln Pro Ile Lys Leu Pro Glu Lys Asp Ser Trp 340 345 350	
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser 355 360 365	
att tat gca ggg Ile Tyr Ala Gly 370	1116
<210> 67 <211> 1119 <212> DNA <213> Human Immunodificiency Virus (HIV)	
<220> <221> CDS <222> (0)(297) <223> HIV Protease	
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cct caa atc act ctt tgg caa cga cca ata gtc aca ata aag ata Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile 1 5 10 15	
Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile	Gly gta 96
Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile 1 5 10 15 ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr	gta 96 Val
Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile 1	gta 96 Val ggg 144 Gly ata 192
Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile 1	gta 96 Val ggg 144 Gly ata 192 Ile aca 240
Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile 1	gta 96 Val 96 Val 96 ggg 144 Gly 192 ata 192 Ile 240 Thr 80 act 288

-122-

Pro	a gga o Gly	a atg / Met 115	: Asp	gg Gly	c cca y Pro	a aaa o Lys	ytt Val	Lys	a caa s Glr	a tgg	g cca p Pro	tto Lei 129	ı Thi	a gaa Glu	a gaa ı Glu	384
aaa Lys	a ata s Ila 130	: Lys	gca Ala	ttg Lei	g gta ı Val	gaa Glu 135	ı Ile	tgt Cys	gca Ala	a gaa a Glu	a ato 1 Met 140	: Glu	a aaçı ı Lys	ggaa Glu	ggg Gly	432
Glr 145	ı Ile	tca Ser	aaa Lys	att Ile	gag Glu 150	Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	: Asn	aat Asr	cca Pro	gta Val	ttt Phe 160	480
gto Val	ata Ile	aag Lys	aaa Lys	Lys 165	: Asp	ggt Gly	act Thr	aac Asn	tgg Trp 170	Arg	aaa Lys	tta Leu	ata Ile	gat Asp 175	ytc Xaa	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	Lys	aga Arg	act Thr	caa Gln	gat Asp 185	ttc Phe	tgg Trp	gaa Glu	att Ile	caa Gln 190	Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	gly	tta Leu	aaa Lys 200	aag Lys	aat Asn	aaa Lys	tca Ser	gta Val 205	Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	ttt Phe	tat Tyr 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gag Glu	aac Asn	ttc Phe	agg Arg	672
aag Lys 225	Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	atg Met 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	att Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
aac Asn	aat Asn	cca Pro 275	gac Asp	ata Ile	gtc Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gca Ala	tct Ser 290	gat Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	His	Arg	Thr	aaa Lys 300	Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	gaa Glu	cat His	cta Leu	ttr Xaa	aag Lys 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aar Lys	aar Lys	yat Xaa 320	960
cag Gln	aaa Lys	gaa Glu	Pro	cca Pro 325	ytc Xaa	ctt Leu	tgg Trp	Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056

-123-

gte Va	c aat l Ası	t ga n Asj 35	p Ile	a caq e Gli	g aag n Lys	g tta S Lev	gtg Val	. Gly	a aaa ⁄ Lys	ttg Lei	g aat 1 Asr	tgg Trp 365	Ala	agt Ser	cag Gln	1104
		r Pro	a ggg													1119
<21 <21	10> 6 11> 1 12> I 13> I	.119 NA	ı Imn	unod	lific	:ienc	y Vi	rus	(HIV	·)				٠		
<22	1> C 2> (0)	.(29 Prote													
<22	_	298)	(.on c		•	vers	e Tr	ansc	ript	ase						
cct	0> 6 caa Gln	ato	act Thr	ctt Leu 5	tgg Trp	caa Gln	cga Arg	ccc Pro	ctc Leu 10	gtc Val	aca Thr	ata Ile	aag Lys	ata Ile 15	gly aaa	48
gga Gly	caa Gln	cta Leu	aaa Lys 20	Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
tta Leu	gaa Glu	gaa Glu 35	Met	aat Asn	ttg Leu	cca Pro	999 Gly 40	aaa Lys	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	gly aaa	144
gga Gly	atc Ile 50	gga Gly	gga Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gag Glu 60	cag Gln	ata Ile	cac His	ata Ile	192
gaa Glu 65	atc	tgt Cys	ggg Gly	cat His	aaa Lys 70	göt Ala	ata Ile	ggt Gly	aca Thr	gtr Xaa 75	tta Leu	ata Ile	gga Gly	ccc Pro	aca Thr 80	240
cct Pro	gtc Val	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggc Gly	tgc Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gag Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	gga Gly	432

-124-

	: Ile					Pro					Asn				ttt Phe 160	480
Āla					Asp					Arg					ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	Leu	gga Gly	576
								Lys					Thr		cta Leu	624
															agg Arg	672
					acc Thr 230										999 Gly 240	720
					aat Asn											768
gca Ala	ata Ile	ttc Phe	caa Gln 260	gct Ala	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
					rtt Xaa											864
					ata Ile											912
					agg Arg 310											960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctc Leu	tgg Trp	Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aag Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	aat Asn	tgg Trp 365	gcg Ala	agt Ser	cag Gln	1104
			eja aaa													1119

-125-

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<210> 69
  <211> 1119
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  <213> Human Immunodificiency Virus (HIV)
  <220>
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  <222> (0)...(297)
  <223> HIV Protease
  <221> CDS
  <222> (298)...(1119)
  <223> Portion of HIV Reverse Transcriptase
  <400> 69
  ect cag atc act ctt tgg caa cga ccc cty gtc aca ata aag ata ggg
                                                                                   48
  Pro Gln Ile Thr Leu Trp Gln Arg Pro Xaa Val Thr Ile Lys Ile Gly
 ggg caa yta aag gaa gct mta tta gay aca gga gca gat gat aca gtg
Gly Gln Xaa Lys Glu Ala Xaa Leu Asp Thr Gly Ala Asp Asp Thr Val
                                                                                  96
 tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa ata ata ggg
                                                                                 144
 Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Ile Ile Gly
 gga att gga ggt ttt atc aaa gta aga gag tat gag cag ata caa gta
                                                                                 192
 Gly Ile Gly Gly Phe Ile Lys Val Arg Glu Tyr Glu Gln Ile Gln Val
 gaa atc tgt gga cat aag gct ata rgt aca gta tta ata gga cct aca
                                                                                 240
 Glu Ile Cys Gly His Lys Ala Ile Xaa Thr Val Leu Ile Gly Pro Thr
 cct gtc aac ata att gga aga aat cta atg act cag att ggt tgc act
Pro Val Asn Ile Ile Gly Arg Asn Leu Met Thr Gln Ile Gly Cys Thr
                                                                                 288
 tta aat ttt ccc att agt cct att gag act gta ccg gta aaa tta aag
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
                                                                                 336
                                     105
 cca gga atg gat ggt cca aga gtt aaa caa tgg cca ttg aca gaa gaa
                                                                                 384
 Pro Gly Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu
          115
                                 120
 aaa ata aaa gca tta gta gaa att tgt aca gaa ttg gaa aag gaa gga
                                                                                 432
 Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Glu Gly
     130
 aaa att tca aaa att ggg cct gaa aat cca tac aat acy ccr gta ttt
                                                                                480
 Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Xaa Xaa Val Phe
gcc ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc
                                                                                528
Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe
                   165
                                          170
```

-126-

a A	iga irg	gaa Glu	ctt Leu	. aat Asn 180	Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	Leu	gga Gly	576
a I	ta le	ccg Pro	cat His 195	ccc Pro	gca Ala	Gly	tta Leu	aag Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctr Xaa	624
g A	at sp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
Ŀ	ag ys 25	tac Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	gga Gly 240	720
a: I:	tt le	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
A.	ca la	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gaa Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
G]	aa ln .	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	car Gln	tac Tyr	atg Met	gat Asp	gac Asp 285	ttg Leu	tat Tyr	gta Val	864
G]	ly :	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	cta Leu	912
ac Ar 30	g (caa Gln	cat His	ctg Leu	tkg Xaa	agg Arg 310	tgg Trp	gga Gly	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
ca Gl	ng a	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cac His	cct Pro 335	gat Asp	1008
aa Ly	a t	rgg Trp	Thr	gta Val 340	cag Gln	cct Pro	ata Ile	Val	ctr Xaa 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gt Va	c a	Asn A	gac Asp 355	ata Ile	cag Gln	aag Lys	Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	Asn	tgg Trp 365	gcg Ala	agt Ser	cag Gln	1104
_	e I			gly Gly													1119

<210> 70 <211> 1119 <212> DNA

<213> Human Immunodificiency Virus (HIV)

<220>

-127-

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-128-

		ĞÌy													agg Arg	672
			gca Ala												999 Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
			caa Gln 260													816
			gac Asp													864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	mta Xaa	999 Gly 295	cag Gln	cat His	aga Arg	rca Xaa	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
			ctg Leu													960
cag Gln	aaa Lys	gaa Glu	ccc Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	car Gln	ccc Pro	ata Ile	gtg Val	ttg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu ,	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
Ile			gly aaa													1119
<210 <211 <212 <213	> 11 > DN	19 A	Immu	nodi	fici	ency	Vir	us (HIV)							
<220 <221 <222 <223	> CD > (0)														
<221: <222: <223:	> (2	98).			Rev	erse	Tra	nscr	ipta	se						

-129-

		0> 7															
											Val					Gly	48
					Glu										Thr	gta Val	96
	tta Leu	gaa Glu	gaa Glu 35	Met	aat Asn	ttg Leu	cca Pro	gga Gly 40	Arg	tgg Trp	aag Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	gtg Val	144
			Gly	ggt Gly												ata Ile	192
	gaa Glu 65	Ile	tgc Cys	gga Gly	cgt Arg	aaa Lys 70	gtt Val	gta Val	ggt Gly	tca Ser	gta Val 75	tta Leu	ata Ile	gga Gly	cct Pro	aca Thr 80	240
				ata Ile													288
				ccc Pro 100													336
				gat Asp													384
				gca Ala													432
	aaa Lys 145	att Ile	aca Thr	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	ccg Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	ata Ile	ttt Phe 160	480
	gcc Ala	ata Ile	aag Lys	aaa Lys	aar Lys 165	aac Asn	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gac Asp 175	ttc Phe	528
			Leu	aat Asn 180	Lys	Arg	Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu		576
	ata Ile	cca Pro	cat His 195	cct Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
4: 7	gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	att Ile	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
1	aar Lys	tat Tyr	act Thr	gca Ala	Phe	acc Thr	ata Ile	cct Pro	agt Ser	Thr	aat Asn	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly	720

-130-

att aga tat cag tat aat gtg ctt cca cag gga tg Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Tr 245 250	g aaa gga tca cca 768 p Lys Gly Ser Pro 255												
gca ata ttc caa agt agc atg aca aaa atc tta gaq Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Gli 260 265													
caa aat ccc gac ata gtt atc tat caa tac gtg gat Gln Asn Pro Asp Ile Val Ile Tyr Gln Tyr Val Asp 275 280													
gga tct gac tta gaa ata gag cag cat aga aca aaa Gly Ser Asp Leu Glu Ile Glu Gln His Arg Thr Lys 290 295 300	s Ile Glu Glu Leu												
aga caa cat ctg tgg aag tgg gga ttt tac aca cca Arg Gln His Leu Trp Lys Trp Gly Phe Tyr Thr Pro 305 310 315													
cag aaa gaa ccc cca ttc ctt tgg atg ggt tat gaa Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu 325 330	a ctc cat cct gat 1008 1 Leu His Pro Asp 335												
aaa tgg aca gta cag cct ata gtg ctg cca gaa aaa Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys 340 345													
gtc aat gac ata caa aag tta gtg gga aaa tta aat Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn 355 360	t tgg gcw agt cag 1104 1 Trp Xaa Ser Gln 365												
att tat cca ggg att Ile Tyr Pro Gly Ile 370	1119												
<210> 72 <211> 1119 <212> DNA <213> Human Immunodificiency Virus (HIV)													
<220> <221> CDS <222> (0)(297) <223> HIV Protease													
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ggg caa tta aag gaa gct cta tta gat aca gga gca Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala 20 25	gat gat aca gta 96 Asp Asp Thr Val 30												

at I	a d le (gaa Glu	gaa Glu 35	Met	aat Asn	ttg Lev	g cca Pro	gga Gly 40	Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	Met	ata : Ile	ggg Gly	14	4
G]	ga a Ly :	att Ile 50	gga Gly	ggt Gly	ttt Phe	rtc Xaa	aaa Lys 55	Val	aga Arg	caa Gln	tat Tyr	gat Asp 60	Gln	gta Val	ccc Pro	ata Ile	19	2
G]	ia a .u] 55	att Ile	tgc Cys	gga Gly	cat His	aaa Lys 70	Ala	ata Ile	ggt Gly	aca Thr	gta Val 75	Leu	ata Ile	gga Gly	cct Pro	aca Thr 80	24	0
Pr	t g	gyc Kaa	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aac Asn	ctg Leu	ttg Leu 90	act Thr	caa Gln	ctt Leu	ggc Gly	tgc Cys 95	act Thr	28	8
t t Le	a a u A	aat Asn	ttt Phe	cca Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	33	6
cc Pr	a g o G	gga Sly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384	4
aa Ly	s I	le 30	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	ctg Leu 140	gaa Glu	aaa Lys	gga Gly	agg Arg	432	2
aa Ly 14	s A	at sn	tac Tyr	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aac Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480	٥
gc Al	c a a I	ta le	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528	3
ag: Ar	ag gG	aa lu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576	5
ata Ile	a co	ro :	cat His 195	cct Pro	gca Ala	gly ggg	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624	ī
gat Ası	v Va	tg q al (ggt Gly	gat Asp	gca Ala	tat Tyr	ttc Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aag Lys	gac Asp	ttc Phe	agg Arg	672	<u> </u>
aag Lys 225	T	at a yr '	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agc Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720)
att Ile	aç Aı	ga 1 rg :	tat Tyr	Gln	tac Tyr 245	aat Asn	gtg Val	ctc Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768	ţ
gcm Xaa	at II	a t le I	Phe (caa Gln 260	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816	;

-132-

caa aat cca gaa ata gtt atc tat caa tac atg gat gat ttg tat gta Gln Asn Pro Glu Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val 275 280 285	864												
ggg tct gac tta gaa ata ggg cag cat aga aca aaa ata gag gaa ctg Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu 290 295 300	912												
aga cga cat ctg ttg aag tgg gga ttt tac aca cca gac aaa aaa cat Arg Arg His Leu Leu Lys Trp Gly Phe Tyr Thr Pro Asp Lys Lys His 305 310 315 320	960												
Cag aaa gaa ccc cca ttc ctt tgg atg ggt tat gag ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008												
aaa tgg aca gta caa cct ata gtg cta cca gag aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350	1056												
gtc aat gac ata cag aag tta gtg gga aag tta aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104												
ata tac gca ggg att Ile Tyr Ala Gly Ile 370	1119												
<210> 73 <211> 1119 <212> DNA <213> Human Immunodificiency Virus (HIV)													
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<221> CDS <222> (298)(1119) <223> Portion of HIV Reverse Transcriptase	٠												
<pre><400> 73 cct caa atc act ctt tgg caa cga ccc ttc gtc aca gta aag ata ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Phe Val Thr Val Lys Ile Gly 1 5 10 15</pre>	48												
ggg cag cta aag gaa gct cta tta gat aca gga gca gat aat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asn Thr Val 20 25 30	96												
tta gaa gaa atg aat tta ccg gga aga tgg aaa cca aaa atg ata ggg Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly 35 40 45	144												
gga att gga ggt ttt atc aaa gta aga cag tat gat cag rta ccc ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Xaa Pro Ile 50 55 60	192												

-133-

	Ile										tta Leu					2	40
					Gly					Thr	cag Gln					21	88
											cca Pro					3:	36
								Lys			cca Pro					38	84
											ctg Leu 140					43	32
											aat Asn					4.8	В0
											aag Lys					52	8 8
											gaa Glu					57	16
											tca Ser					62	?4
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	67	12
											aat Asn					72	:0
											tgg Trp					76	8
											gag Glu					81	.6
cag Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tac Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gac Asp 285	ttg Leu	tat Tyr	gta Val	86	4
											aaa Lys 300					91	.2

-134-

Arg Gln His Leu Leu Lys Trp Gly Phe Tyr Thr Pro Asp Lys Lys His 305 310 315 320	960
cag aaa gaa cca cca ttc ctt tgg atg ggk tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Xaa Tyr Glu Leu His Pro Asp 325 330 335	1008
aaa tgg aca gta cag cct ata gtg ctg cca gaa aar gac agc tgg act Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350	1056
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
att tac cca ggg att Ile Tyr Pro Gly Ile 370	1119
<210> 74 <211> 1116 <212> DNA <213> Human Immunodificiency Virus (HIV)	
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<221> CDS <222> (298)(1116) <223> Portion of HIV Reverse Transcriptase	
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cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag gtc ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Val Gly	48 96
cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag gtc ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Val Gly 1 5 10 15 ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val	
cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag gtc ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Val Gly 1	96
cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag gtc ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Val Gly 1	96 144

	tta Leu	aat Asr	ttt Phe	Pro 100	Ile	agt Ser	cct Pro	att Tle	gaa Glu 105	Thr	gta Val	cca Pro	gta Val	aaa Lys 110	Lev	aag Lys	336
			atg Met 115	Asp					Lys					Thr		gaa Glu	384
			aaa Lys														432
	aaa Lys 145	Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
			aag Lys			Asp											528
	aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
			cat His 195														624
	gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gaa Glu	ttc Phe	agg Arg	672
	aag Lys 225	tac Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	gga Gly 240	720
	att Ile	aga Arg	tac Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	ccc Pro	cag Gln 250	Gly 999	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
	gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	agg Arg	aaa Lys	816
(caa Gln	aat Asn	cca Pro 275	gac Asp	Ile	gtt Val	Ile	Tyr	Gln	Tyr	Met	gat Asp	Asp	ttg Leu	tat Tyr	gta Val	864
Ć	gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
7	aga Arg 805	cag Gln	cat His	ctg Leu	ttg Leu	agg Arg 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aag Lys	cat His 320	960
Ċ	eag Sln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	Met	ggt Gly 330	tat Tyr	gag Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008

-136-

aaa tgg aca gta cag cct ata gtg ctg cca gaa aag gat agc tgg act Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350	1056													
gtc aat gac ata cag aag tta gtg gga aaa tta aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104													
att tat gca ggg Ile Tyr Ala Gly 370	1116													
<210> 75 <211> 819 <212> DNA <213> Human Immunodificiency Virus (HIV)														
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gat ggc cca aaa gtt aaa caa tgg cca tta aca gag gaa aaa ata aaa Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys 20 25 30	96													
gca ttg gta gaa att tgt aca gaa atg gaa aag gaa gga aaa att tca Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly Lys Ile Ser 35 40 45	144													
aaa att ggg cct gaa aat cca tac aat act cca gta ttt gcc ata aag Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe Ala Ile Lys 50 55 60	192													
aaa aag gac agt act aaa tgg aga aaa tta gta gat ttc aga gaa ctt Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe Arg Glu Leu 65 70 75 80	240													
aat aar aga act caa gat ttc tgg gaa gtt caa tta gga ata cca cat Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly Ile Pro His 85 90 95	288													
ccc tca ggg tta aaa aag aay aaa tca gta aca gta ttg gat gtg ggt Pro Ser Gly Leu Lys Lys Asn Lys Ser Val Thr Val Leu Asp Val Gly 100 105 110	336													
gat gca tat ttt tca gtt ccy tta gat aaa gac ttc agg aag tat act Asp Ala Tyr Phe Ser Val Xaa Leu Asp Lys Asp Phe Arg Lys Tyr Thr 115 120 125	384													
gca ttt acc ata cct agt ata aac aat gag aca cca ggg att agr tat Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile Xaa Tyr 130 135 140	432													

-137-

cag tac Gln Tyr 145	aat Asn	gtg Val	ctt Leu	cca Pro 150	caa Gln	gga Gly	tgg Trp	aaa Lys	gga Gly 155	tca Ser	cca Pro	gca Ala	ata Ile	ttc Phe 160		480
caa agt Gln Ser		Met														528
gac ata Asp Ile	Val	atc Ile 180	tat Tyr	caa Gln	tac Tyr	gtg Val	gat Asp 185	gat Asp	ttg Leu	tat Tyr	gta Val	gga Gly 190	tct Ser	gac Asp		576
tta gaa Leu Glu	ata q Ile (195	gag g Glu (gag Glu	cat His	aga Arg	aca Thr 200	aaa Lys	ata Ile	gag Glu	gaa Glu	ctg Leu 205	agr Xaa	vrg Xaa	cat His		624
ctg tta Leu Leu 210															1	672
cct cca Pro Pro 225			Trp												•	720
gta cag Val Gln	cct a	Ile I	aag Lys 245	ctg Leu	cca Pro	gaa Glu	aaa Lys	gac Asp 250	agc Ser	tgg Trp	act Thr	gtc Val	aat Asn 255	gac Asp	•	768
ata cag Ile Gln	Lys I	ta g Leu V 260	gtg /al	gga Gly	aaa Lys	ttg Leu	aat Asn 265	tgg Trp	gca Ala	agt Ser	cag Gln	att Ile 270	tat Tyr	gca Ala	8	316
gl ^à aaa															8	319
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<222> (0 <223> Po <400> 76	rtion		HIV	Rev	erse	Tra	nscr	ipta	se							
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gat ggc Asp Gly	Pro L	aa g ys X 20	ty a aa I	aaa (Lys (caa (Gln :	tgg (Trp :	cca Pro 1 25	tta . Leu '	aca (Thr	gaa Glu	gaa Glu	aaa Lys 30	ata Ile	aga Arg		96
gca tta Ala Leu	gta g Val G 35	aa a lu I	tt t le C	gt a Cys 1	aca c	gaa a Glu I 40	atg (Met (gaa a Glu i	aag (Lys (gaa Glu	gga Gly :	aaa Lys	att Ile	tca Ser	1	44

WO 01/35316 PCT/US00/30863

-138-

•																
aa <i>a</i> Lys	att Ile 50	Gly	cct Pro	gaa Glu	aat Asn	cca Pro 55	tac Tyr	aat Asn	act Thr	cca Pro	gtg Val 60	ttt Phe	gct Ala	ata Ile	aag Lys	192
aaa Lys 65	aaa Lys	gac Asp	agt Ser	act Thr	aar Lys 70	tgg Trp	aga Arg	aaa Lys	ttg Leu	gta Val 75	gat Asp	ttc Phe	aga Arg	gaa Glu	ctt Leu 80	240
aat	aag Lys	aga Arg	act Thr	caa Gln 85	gac Asp	ttc Phe	tgg Trp	gaa Glu	gtt Val 90	caa Gln	tta Leu	gga Gly	ata Ile	cca Pro 95	cat His	288
ccc Pro	tca Ser	ggg ggg	tta Leu 100	aaa Lys	aag Lys	aaa Lys	aaa Lys	tca Ser 105	gta Val	aca Thr	gta Val	ctg Leu	gat Asp 110	gtg Val	ggt Gly	336
	gca Ala															384
	ttt Phe 130															432
	tac Tyr															480
	agt Ser															528
	ata Ile															576
	gaa Glu															624
	ttg Leu 210															672
	ccc Pro															720
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gly aaa																819

WO 01/35316 PCT/US00/30863

-139-

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Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly
                                                                                      48
  ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta
                                                                                      96
  Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val
  tta gaa gac atg aat ttg cca ggg aga tgg aaa cca aaa atg ata ggg
                                                                                     144
  Leu Glu Asp Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly
             35
  gga att gga ggt ttt atc aaa gta aga cag tat gat cag ata cct ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Pro Ile
                                                                                     192
  gaa atc tgc gga cat aaa gct gta ggt aaa gta tta gta gga cct aca
                                                                                     240
  Glu Ile Cys Gly His Lys Ala Val Gly Lys Val Leu Val Gly Pro Thr
  cct gtc aac ata att gga aga aat ctg ttg act caa ctt ggt tgc act
                                                                                     288
  Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Leu Gly Cys Thr
                                              90
 tta aat ttt cct att agt cct att gaa act gta cca gta aaa tta aag
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
                                                                                     336
 cca gga atg gat ggc cca aaa gtt aag caa tgg cca ttg aca gaa gaa
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu
                                                                                     384
 aaa ata aaa gca tta gta gaa att tgt aca gaa atg gag aag gaa ggg
                                                                                     432
 Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly
      130
                              135
                                                       140
 aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt
                                                                                     480
 Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
 gct ata aag aaa aaa aac agt act aga tgg aga aaa tta gta gat ttc
                                                                                     528
 Ala Ile Lys Lys Lys Asn Ser Thr Arg Trp Arg Lys Leu Val Asp Phe
                                            170
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-140-

														Xaa	nnn Xaa	576	
Xaa			Xaa			twa Xaa									ctg Leu	624	
		Gly				ttc Phe 215										672	
	Tyr					ata Ile										720	
						gtg Val										768	
						atg Met										816	
						atc Ile										864	
						999 Gly 295										912	
	Gln					tgg Trp										960	
						ctt Leu										1008	
						ata Ile										1056	
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agc Ser	cag Gln	1104	
Ile	tat Tyr 370															1116	

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<213> Human Immunodificiency Virus (HIV)

-141-

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				Glu										Thr	gta Val	96
tta Leu	gaa Glu	gac Asp 35	atg Met	gat Asp	ttg Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	gly ggg	144
gga Gly	att Ile 50	Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aaa Lys	cag Gln	tat Tyr	gat Asp 60	cag Gln	ata Ile	ccc Pro	ata Ile	192
gaa Glu 65	Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gtt Val	ata Ile	ggt Gly	aca Thr	gta Val 75	Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
cct Pro	gtc Val	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	ctt Leu	ggt Gly	tgc Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aga Arg	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	ttg Leu	gta Val	gaa Glu 135	ata Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	Gly ggg	432
aaa Lys 145	Ile	tca Ser	Lys	att Ile	Gly	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	acr Xaa	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	arg Xaa	aaa Lys	aaa Lys 165	gaa Glu	agc Ser	tct Ser	agc Ser	tct Ser 170	aaa Lys	tgg Trp	aga Arg	aaa Lys	tta Leu 175	gta Val	528
gat Asp	ttc Phe	aga Arg	gaa Glu 180	ctt Leu	aat Asn	aar Lys	aga Arg	act Thr 185	caa Gln	gac Asp	ttt Phe	ttk Xaa	gaa Glu 190	gtt Val	caa Gln	576
tta Leu	gga Gly	ata Ile 195	cca Pro	cat His	ccc Pro	gca Ala	999 Gly 200	tta Leu	aag Lys	aag Lys	aaa Lys	aaa Lys 205	tca Ser	gya Xaa	aca Thr	624

-142-

rta Xaa	a ttg a Leu 210	. Asp	gtg Val	ggt Gly	gat Asp	gca Ala 215	Tyr	ttt Phe	tca Ser	gtt Val	ccc Pro 220	tta Leu	gat Asp	raa Xaa	gac Asp	672
tto Phe 225	Arg	aag Lys	tat Tyr	act Thr	gca Ala 230	ttt Phe	acc Thr	ata Ile	cct Pro	agt Ser 235	ata Ile	aac Asn	aat Asn	gag Glu	aca Thr 240	720
Pro	Gly Gly	att Ile	aga Arg	tat Tyr 245	cag Gln	tac Tyr	aat Asn	gtg Val	ctt Leu 250	cca Pro	cag Gln	gga Gly	tgg Trp	aaa Lys 255	gga Gly	768
tca Ser	cca Pro	gct Ala	ata Ile 260	ttc Phe	caa Gln	agt Ser	agc Ser	atg Met 265	aca Thr	aaa Lys	atc Ile	tta Leu	gag Glu 270	cct Pro	ttt Phe	816
aga Arg	aaa Lys	caa Gln 275	aat Asn	cca Pro	gay Asp	ata Ile	gtt Val 280	atc Ile	tat Tyr	caa Gln	tac Tyr	atg Met 285	gat Asp	gat Asp	ttg Leu	864
tat Tyr	gta Val 290	gga Gly	tct Ser	gay Asp	tta Leu	gaa Glu 295	ata Ile	gag Glu	cag Gln	cat His	aga Arg 300	ata Ile	aaa Lys	ata Ile	gag Glu	912
gaa Glu 305	ctg Leu	aga Arg	caa Gln	yat Xaa	ytg Xaa 310	tgg Trp	arg Xaa	tgg Trp	ggr Xaa	ttt Phe 315	tac Tyr	aca Thr	cca Pro	gac Asp	aaa Lys 320	960
aaa Lys	cat His	cag Gln	aaa Lys	gaa Glu 325	cct Pro	cca Pro	ttc Phe	cat His	tgg Trp 330	atg Met	ggt Gly	tat Tyr	gaa Glu	ctc Leu 335	cat His	1008
cct Pro	gat Asp	aaa Lys	tgg Trp 340	aca Thr	gta Val	cag Gln	cct Pro	ata Ile 345	gtg Val	ctg Leu	cca Pro	gaa Glu	aaa Lys 350	gac Asp	agc Ser	1056
tgg Trp	act Thr	gtc Val 355	aat Asn	gac Asp	ata Ile	cag Gln	aag Lys 360	tta Leu	gtg Val	gga Gly	Lys	ttg Leu 365	aat Asn	tgg Trp	gca Ala	1104
agt Ser	cag Gln 370	att Ile	tat Tyr	gca Ala	ggr Xaa											1122
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-143-

		0 > 7																
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				aag Lys 20	Glu										Thr	gta Val		96
									Arg							gly aaa		144
			Gly	ggt												ata Ile		192
				Gly ggg														240
				ata Ile														288
				ccc Pro 100														336
				gat Asp														384
				gca Ala														432
				aaa Lys														480
				aaa Lys														528
				aat Asn 180	Lys		Thr	Gln	Āsp	Phe	Trp	Ğlu						576
				ccc Pro														624
	Asp			gat Asp														672
1	aag Lys 225	tat Tyr	act Thr	gca Ala	Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	Thr	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	,	720

-144-

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gca Ala															aaa Lys	816
caa Gln																864
gga Gly																912
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cag (Gln)																1008
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gtc a Val i																1104
att t Ile 1																1116
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Gly G	ag (Sln 1	cta a Leu 1	aag (Lys (gag Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96

-145-

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		Gly										Gln			ata Ile		192
	ı Ile										Leu				aca Thr 80		240
			ata Ile		Gly										Thr	•	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys		336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc	cca Pro	aga Arg	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu		384
			gca Ala														432
aaa Lys 145	Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	rta Xaa	ttt Phe 160		480
			aaa Lys														528
			aat Asn 180														576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	gly aaa	ttg Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu		624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttc Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gaa Glu	gac Asp	ttc Phe	aga Arg		672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240		720
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gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys		816

-146-

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gga tct gac tta gaa ata ggg cag cat agg aca aaa ata gag gaa ctg Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu 290 295 300	912
aga caa cat ttg ttg aag tgg ggg ttt acc aca cca gac aaa aaa cat Arg Gln His Leu Leu Lys Trp Gly Phe Thr Thr Pro Asp Lys Lys His 305 310 315 320	960
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008
aaa tgg aca gtg cag cct ata gtg tta ccg gaa aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350	1056
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
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tta gaa gaa ata aat ttg cca gga aga tgg aaa cca aaa atg ata ggg Leu Glu Glu Ile Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly 35 40 45	144
gga att gga ggt ttt atc aaa gta aaa cag tat gat caa ata ccy rta Gly Ile Gly Gly Phe Ile Lys Val Lys Gln Tyr Asp Gln Ile Xaa Xaa 50 55 60	192

-147-

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	cct Pro	gto Val	c aa l As	c at n Il	a ati e Ile 85	≥ Gl	a agi y Xaa	c aat a Asi	t cto n Lev	tto Lev 90	ı Thi	cag Glr	g att	gg ¹	t tgo y Cys 95	c act s Thr		288
	tta Lev	a aat 1 Asr	tt 1 Ph	t cce e Pro 10	o Ile	agt Sei	cct r Pro	att Ile	gaa Glu 105	Thr	gta Val	cca Pro	gta Val	a aaa . Lys 110	s Lev	a aag 1 Lys		336
	cca Pro	gga Gly	Mei	: As	ggo Gly	cca Pro	a aaa o Lys	gtt Val	Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	Thi	a gaa Glu	a gaa 1 Glu		384
	aaa Lys	ata Ile 130	: Lys	a gca s Ala	a tt <u>c</u> a Leu	gta Val	gaa Glu 135	Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	Glu	aag Lys	g gaa Glu	a gga a Gly		432
	aaa Lys 145	Ile	tca Ser	aga Arg	att Ile	999 Gly 150	Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	Asn	act Thr	cca Pro	gta Val	ttt Phe 160		480
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j	agg Arg	gaa Glu	ctt Leu	aat Asn 180	Lys	agg Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly		576
ā	ata [le	cca Pro	cat His 195	Pro	gca Ala	Gly aaa	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu		624
Į	jat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gaa Glu	ttc Phe	agg Arg		672
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a	le	aga Arg	tat Tyr	caa Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	caa Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro		768
9 A	ca la	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cca Pro	ttt Phe 270	aga Arg	aaa Lys		816
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WO 01/35316 PCT/US00/30863

-148-

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gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
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-149-

																226
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															gaa Glu	384
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	ata Ile															528
	gaa Glu															576
	cca Pro															624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gam Xaa	ttc Phe	agg Arg	672
	tat Tyr															720
	aga Arg															768
	ata Ile															816
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aga Arg 305	cag Gln															960
cag Gln	aaa Lys															1008

WO 01/35316 PCT/US00/30863

-150-

aaa tgg ac Lys Trp Th	a gta cag c Val Glr 340	g cct ata n Pro Ile	aaa cto Lys Let 345	ı Pro Gl	a aaa gad u Lys Asj	agc to Ser T 350	gg act Trp Thr	1056
gty aat gad Xaa Asn Asn 355	o Ile Glm	g aag tta Lys Leu	gtg gga Val Gly 360	a aaa tt: / Lys Xaa	r aat tgg a Asn Trp 369	Ala S	igt cag Ser Gln	1104
att tat gca Ile Tyr Ala 370								1116
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tta gaa gac Leu Glu Asp 35	Met Ser							144
gga att gga Gly Ile Gly 50								192
gaa atc tgt Glu Ile Cys 65					Leu Val			240
cct gtc aac Pro Val Asn						Gly C		288
tta aat ttt Leu Asn Phe								336
cca gga atg Pro Gly Met 115								384

aaa Lys	ata Ile 130	: Lys	gca Ala	tta Lei	gta Val	gaa Glu 135	Ile	tgt Cys	aca Thr	gaa Glu	atc Met 140	: Glu	aag Lys	gaa Glu	gga Gly	432
	Ile					Pro					Asn				ttt Phe 160	480
gco					Asp					Arg					ttt Phe	528
				Lys					Phe						gga Gly	576
ata Ile	cca Pro	cat His 195	cca Pro	gca Ala	ggg	tta Leu	aaa Lys 200	Lys	aaa Lys	aag Lys	tca Ser	gta Val 205	Thr	gtg Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gaa Glu	ttc Phe	agg Arg	672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	ccc Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	ccc Pro	agg Arg 240	720
gtt Val	aga Arg	tat Tyr	caa Gln	tac Tyr 245	aat Asn	gta Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	tat Tyr	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gaa Glu	ccc Pro	ttc Phe 270	aga Arg	aaa Lys	816
caa Gln	aac Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gac Asp 285	tta Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gag Glu	ata Ile	gga Gly 295	cag Gln	cat His	aga Arg	gca Ala	aaa Lys 300	ata Ile	gag Glu	gac Asp	cta Leu	912
aga Arg 305	gca Ala	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	ggg ggg	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	ccc Pro	cca Pro 325	ttt Phe	ctc Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp		gta Val 340	cag Gln	cct Pro	ata Ile	gwg Xaa	cta Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aaa Lys	Leu	gta Val 360	gga Gly	aaa Lys	tta Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104

-152-

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<221> CDS <222> (298)(1116) <223> Portion of HIV Re	everse Transcriptase	·	
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ggg caa cta atg gaa gct Gly Gln Leu Met Glu Ala 20	c cta tta gat aca gg a Leu Leu Asp Thr Gl 25	a gca gat gat aca y Ala Asp Asp Thr 30	gta 96 Val
tta gaa gac ata aat tto Leu Glu Asp Ile Asn Leu 35	g cca gga aga tgg aa n Pro Gly Arg Trp Ly 40	a cca aaa ata ata s Pro Lys Ile Ile 45	999 144 Gly
gga att ggt ggt ttt gto Gly Ile Gly Gly Phe Val 50	aaa gtg aga cag ta Lys Val Arg Gln Ty 55	t gat cag gta ccc r Asp Gln Val Pro 60	ata 192 Ile
gaa atc tgt gga cat aaa Glu Ile Cys Gly His Lys 65 70	Val Ile Gly Thr Va	l Leu Val Gly Pro	aca 240 Thr 80
cct acc aac gta gtt gga Pro Thr Asn Val Val Gly 85	aga aat ctg atg act Arg Asn Leu Met Th	t cag att ggc tgc r Gln Ile Gly Cys 95	acy 288 Xaa
tta aat ttt cct att agt Leu Asn Phe Pro Ile Ser 100	cct att gaa act gta Pro Ile Glu Thr Va 105	a cca gta aaa tta l Pro Val Lys Leu 110	aag 336 Lys
cca gga atg gat ggc cca Pro Gly Met Asp Gly Pro 115	aaa gtt aaa caa tgg Lys Val Lys Gln Trp 120	g cca ttg acg gaa p Pro Leu Thr Glu 125	gaa 384 Glu
aaa ata aaa gca tta gta Lys Ile Lys Ala Leu Val 130	gaa att tgt aca gaa Glu Ile Cys Thr Glu 135	a ctg gaa aag gat 1 Leu Glu Lys Asp 140	gga 432 Gly
aaa att tca aaa att ggg Lys Ile Ser Lys Ile Gly 145 150	cct gaa aat cca tat Pro Glu Asn Pro Tyr 155	Asn Thr Pro Ile	ttt 480 Phe 160

-153-

gc Al	c ata a Ile	a aag E Lys	, aaa : Lys	aag Lys 165	Asn	agt Ser	gat Asp	aaa Lys	tgg Trp 170	Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
ag; Ar	a gaa g Glu	ctt Leu	aat Asn 180	. Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	a cca e Pro	cat His 195	Pro	gca Ala	Gly 999	tta Leu	aaa Lys 200	aag Lys	aat Asn	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624.
gat Asp	ata Ile 210	Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	att Ile	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttt Phe	agg Arg	672
aac Lys 225	tat Tyr	act Thr	gca Ala	ttc Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
gtt Val	aga Arg	tat Tyr	Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aag Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agc Ser	agc Ser	atg Met	acc Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
cag Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tgc Cys 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctr Xaa	912
Arg 305	aat Asn	Xaa	Leu	Trp	Lys 310	Trp	Gly	Phe	Tyr	Thr 315	Pro	Āsp	Lys	Lys	Tyr 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	ccc Pro	ata i	Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag : Lys :	Leu '	gtg Val 360	gga Gly	aaa Lys	tta Leu .	Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
	tat Tyr 370															1116

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-154-

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  <223> HIV Protease
_...<221> CDS
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  <223> Portion of HIV Reverse Transcriptase
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                                                                                     48
                                                                                     96
  ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta
  Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val
  tta gaa gaa atg aat ttg cca ggg aga tgg aaa cca aaa atg ata ggg
                                                                                    144
  Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly
 gga att gga ggt ttt atc aaa gta aga cag tat gat cag gta agc ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Val Ser Ile
                                                                                    192
 gaa atc tgt gga cat aaa gct ata ggt aca gta tta ata gga ccc acc
                                                                                    240
 Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Ile Gly Pro Thr
 cct gtc aac ata att gga aga aat ctg ttg act cag ctt ggt tgc act
                                                                                    288
 Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Leu Gly Cys Thr
 tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
                                                                                    336
 cca gga atg gat ggc cca aga gtt aaa caa tgg cca ttg aca gaa gaa
Pro Gly Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu
                                                                                    384
                                  120
 aaa ata aaa gca tta gta gaa att tgt aca gaa atg gag aag gaa ggr
                                                                                    432
 Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Xaa
     130
                             135
 aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt
                                                                                    480
 Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
 145
 gcc ata aar aaa aaa gac agt act aaa tgg aga aag tta gta gat ttc
                                                                                    528
 Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe
 aga gaa ctt aat aaa ara act caa gac ttc tgg gaa gtt caa tta gga
                                                                                   576
 Arg Glu Leu Asn Lys Xaa Thr Gln Asp Phe Trp Glu Val Gln Leu Gly
                                       185
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-155-

			Pro								tca Ser				ctg Leu	624
		ĞĨy									gay Asp 220					672
	Tyr										aat Asn					720
											tgg Trp					768
											gag Glu					816
											gat Asp					864
											aaa Lys 300					912
											cca Pro					960
											gaa Glu					1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	wtg Xaa	ctg Leu 345	cca Pro	gac Asp	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtm Xaa	aat Asn	gac Asp 355	ata Ile	cag Gln	aar Lys	tta Leu	gta Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gcg Ala	agt Ser	cag Gln	1104
	tac Tyr 370															1116
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	> Hu		Immu	nodi	fici	ency	Vir	us (HIV)							
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-156-

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-157-

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att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	Pro	768
agca Ala	ata Ile	ttc Phe	caa Gln 260	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	ccc Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gaa Glu	ata Ile	gtt Val	atc Ile	tgt Cys 280	cag Gln	tac Tyr	atg Met	gat Asp	gac Asp 285	ttg Leu	tat Tyr	gta Val	864
gca Ala	tct Ser 290	.gat Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	gta Val	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	gly aaa	ttt Phe	ttc Phe	aca Thr 315	cca Pro	gac Asp	gaa Glu	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gta Val	ctg Leu 345	cca Pro	gac Asp	caa Gln	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gat Asp 355	ata Ile	cag Gln	aag Lys	Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	caa Gln	1104
att Ile	tac Tyr 370	cca Pro	Gly 999													1116
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-158-

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	tta Le:	a gaa u Gli	a ga u Gl 3	u Me	g aan t Asi	t tte	g tca u Sei	a gga Gly	Arg	tgg Trp	g aaa b Lys	a cca s Pro	a aaa b Lys 45	s Met	g ata t Ile	a ggg	144
***	ġga Gly	a att 7 Ile 50	= G1	a gg y Gl	t tti y Phe	t ato	aaa E Lys 55	: Val	a aga Arg	cag Glr	g tat 1 Tyr	gat Asp 60	Glr	g ata n Ile	e ccc	ata Ile	192
	gag Glu 65	ı Ile	tg Cy:	t gga s Gly	a cat / His	aaa Lys 70	. Ala	gta Val	ggt Gly	aca Thr	gta Val	Leu	ı gta	gga Gly	a cct	aca Thr 80	240
	cct Pro	gto Val	aad Asi	c ata n Ile	a att E Ile 85	: Gly	agr Xaa	aat Asn	ctg Leu	ttg Leu 90	Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	acc	288
	tta Leu	aat Asn	ttt Phe	e Pro) Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	Thr	gta Val	cca Pro	gta Val	aaa Lys 110	Leu	aag Lys	336
	cca Pro	gga Gly	ato Met	: Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	Thr	gaa Glu	gaa Glu	` 384
;	aaa Lys	ata Ile 130	Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	Gly aaa	432
J	aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	ata Ile	ttt Phe 160	480
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P	aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
Į	lta	cca Pro	cat His 195	ccy Xaa	gca Ala	ggg Gly	ttg Leu	aar Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
9 A	at sp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttc Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gaa Glu	gay Asp	ttc Phe	aga Arg	672
بد	ag ys 25	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
g V	tt al	aga Arg	tat Tyr	car Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	Pro	cag Gln 250	gga Gly	tgg Trp	aag Lys	gga Gly	tca Ser 255	cca Pro	768

-159-

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	gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	car Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ttg Leu	912
	aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	gga Gly	tta Leu	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
	cag Gl _i n	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
	aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
	gtc Val	aat Asn	gat Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
			gca Ala				•						-				1116
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,	<222	> CD > (0	S) V Pr	(297 otea) se												
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Ċ	ggg (Sly (caa o Gln 1	cta a Leu 1	agg Arg : 20	raa Xaa .	gct (Ala :	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
İ	ta g Leu (gaa g Blu <i>l</i>	gac a Asp 1 35	ata q [le (gaa Glu	ttg (Leu 1	cca Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	gly aaa	144

-160-

gg; Gl;	a att y Ile 50	e Gly	a ggt / Gly	ttt Phe	gtc Val	aaa Lys 55	Val	aga Arg	caa Gln	tat Tyr	gat Asp 60	Gln	ata Ile	ccc Pro	ata Ile	192
gaa Glu 65	ı Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gtt Val	ata Ile	ggt Gly	aca Thr	gta Val 75	Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
		aac Asn			Gly					Thr					Thr	288
tta Lev	a aat 1 Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
		atg Met 115	Asp													384
aaa Lys	ata Ile 130	gaa Glu	gca Ala	tta Leu	atr Xaa	gaa Glu 135	att Ile	tgt Cys	gma Xaa	ttt Phe	ttg Leu 140	gaa Glu	aag Lys	gaa Glu	gga Gly	432
	Ile	tca Ser														480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gga Gly	ggt Gly	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	ata Ile	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aaa Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	gcg Ala	GJA aaa	tta Leu	aaa Lys 200	aag Lys	aay Asn	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
		ggt Gly														672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	act Thr 230	ata Ile	cct Pro	agt Ser	aca Thr	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
att Ile	aga Arg	tac Tyr	Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttt Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	ccc Pro	ttt Phe 270	aga Arg	aag Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	Ile	twt Xaa 280	caw Xaa	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864

-161-

Gly Ser Asp Leu Glu Ile Gly Lys His Arg Glu Lys Ile Glu Glu Leu 290 295 300	912
aga caa cat ctg tgg aag tgg gga ttt tac aca cca gac gaa aaa cat Arg Gln His Leu Trp Lys Trp Gly Phe Tyr Thr Pro Asp Glu Lys His 305 310 315 320	960
Cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat ctt gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Leu Asp 325 330 335	1008
aaa tgg aca gta cag cct ata gtg ctg cca gaa aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350	1056
gtc aat gac ata cag aag tta gtg gga aaa tta aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
att tat gca ggg Ile Tyr Ala Gly 370	1116
<210> 89 <211> 1116 <212> DNA <213> Human Immunodificiency Virus (HIV)	
<220>	
<221> CDS <222> (0)(297) <223> HIV Protease	·
<222> (0)(297)	
<222> (0)(297) <223> HIV Protease <221> CDS <222> (298)(1116)	48
<pre><222> (0)(297) <223> HIV Protease <221> CDS <222> (298)(1116) <223> Portion of HIV Reverse Transcriptase <400> 89 cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag ata ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly</pre>	48 96
<pre><222> (0)(297) <223> HIV Protease <221> CDS <222> (298)(1116) <223> Portion of HIV Reverse Transcriptase <400> 89 cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag ata ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly 1</pre>	
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-162-

					Gly					Thr					act Thr		288
tta Lev	aat Asn	ttt Phe	ccc Pro 100	$Il\epsilon$	agt Ser	cct Pro	att Ile	gaa Glu 105	Pro	gta Val	cca Pro	gta Val	aaa Lys 110	Leu	aag Lys		336
CCa	gga Gly	atg Met 115	Asp	ggc	cca Pro	aaa Lys	gtt Val 120	Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	Thr	gaa Glu	gaa Glu		384
aaa Lys	ata Ile 130	Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	ctg Leu 140	Ğlu	aaa Lys	gaa Glu	Gly 999		432
	Ile		aaa Lys												ttt Phe 160		480
															ttc Phe		528
aga Arg	gaa Glu	ctg Leu	aat Asn 180	aag Lys	aaa Lys	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly		576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	Gly 999	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	acg Thr	gta Val	ctg Leu		624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg		672
aaa Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	aca Thr	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	•	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro		768
gca Ala	ata Ile	ttt Phe	caa Gln 260	cat His	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys		816
cag Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gac Asp 285	ttg Leu	tat Tyr	gta Val		864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu		912
aga Arg 305	gaa Glu	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320		960

-163-

	g aaa n Lys	a gaa s Glu	cct Pro	cca Pro 325	Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aa Ly	a tgg s Trp	g aca Thr	gta Val 340	Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gte Va	c aat l Asr	gat Asp 355	Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
	tate Tyr 370	Ala														1116
<21 <21	.0> 9 .1> 1 .2> D .3> H	116 NA	Imm	ınodi	ifici	iency	y Vi:	rus	(HIV))						
<22	0> 1> C 2> (3> H	0)	-													
<22	1> C 2> (3> P	298)				verse	e Tra	insci	ripta	ıse						
cct	0 > 9															
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1 gga	Gln cag Gln	Ile	aag	Leu 5 gaa	Trp gct	Gln yta	Arg	Pro	Xaa 10 aca	Val gga	Thr	Ile	Lys	Val 15 aca	Gly	48 96
gga Gly tta	Gln	cta Leu	aag Lys 20 atg	Leu 5 gaa Glu aac	gct Ala	Gln yta Xaa cca	tta Leu gga	Pro gat Asp 25	Xaa 10 aca Thr	yal gga Gly	Thr gca Ala cca	Ile gat Asp	Lys gat Asp 30	Val 15 aca Thr	Gly gta Val	
gga Gly tta Leu	cag Gln gaa	cta Leu gaa Glu 35	aag Lys 20 atg Met	Leu 5 gaa Glu aac Asn	gct Ala ttg Leu	yta Xaa cca Pro	tta Leu gga Gly 40	gat Asp 25 aaa Lys	Xaa 10 aca Thr tgg Trp	yal gga Gly aaa Lys	Thr gca Ala cca Pro	gat Asp aaa Lys 45	gat Asp 30 ata Ile	Val 15 aca Thr ata Ile	gta Val 999 Gly	96
gga Gly tta Leu gga Gly	cag Gln gaa Glu att Ile	cta Leu gaa Glu 35 gga Gly	aag Lys 20 atg Met Gly	gaa Glu aac Asn ttt Phe	gct Ala ttg Leu gtc Val	yta Xaa cca Pro aga Arg 55	tta Leu gga Gly 40 gta Val	gat Asp 25 aaa Lys aga Arg	Xaa 10 aca Thr tgg Trp caa Gln	yal gga Gly aaa Lys tat Tyr	Thr gca Ala cca Pro gat Asp 60 tta	gat Asp aaa Lys 45 cag Gln	gat Asp 30 ata Ile gta Val	Val 15 aca Thr ata Ile cct Pro	gta Val ggg Gly gta Val	96 144
gga Gly tta Leu gga Gly gaa Glu 65	cag Gln gaa Glu att Ile 50	cta Leu gaa Glu 35 gga Gly tgt Cys	aag Lys 20 atg Met ggt Gly gga Gly	gaa Glu aac Asn ttt Phe cat His	gct Ala ttg Leu gtc Val aaa Lys 70	yta Xaa Cca Pro aga Arg 55 gct Ala	tta Leu gga Gly 40 gta Val ata Ile	gat Asp 25 aaa Lys aga Arg ggt Gly	Xaa 10 aca Thr tgg Trp caa Gln tca Ser	gga Gly aaa Lys tat Tyr gta Val 75 act	gca Ala cca Pro gat Asp 60 tta Leu	gat Asp aaa Lys 45 cag Gln gta Val	gat Asp 30 ata Ile gta Val gga Gly	Val 15 aca Thr ata Ile cct Pro	gta Val ggg Gly gta Val aca Thr 80	96 144 192

-164-

Pro	a gga o Gly	a ato Met	: Asp	Gly	c cca / Pro	aaa Lys	gtt Val 120	. Lys	caa Gln	tgg Trp	p cca	ttg Lei 125	Thi	a gaa Glu	a gaa ı Glu	384
aaa Lys	a ata 5 Ile 130	: Lys	gca Ala	tta Lev	gta Val	gar Glu 135	att	tgt Cys	aca Thr	gaa Glu	yto Xaa 140	Glu	aaa Lys	gaa Glu	a gga a Gly	432
aag Lys 145	: Ile	tca Ser	aaa Lys	att	999 Gly 150	Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aag Lys 165	Asn	agt Ser	gat Asp	aga Arg	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	cct Pro	gga Gly	gly ggg	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	cta Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttc Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gaa Glu	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
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gca Ala	ata Ile	tty Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	agg Arg	aag Lys	816
maa Xaa	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	att Ile 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gtr Xaa	864
gga Gly	tct Ser 290	gat Asp	tta Leu	gaa Glu	ata Ile	gar Glu 295	cag Gln	cay His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	gat Asp	cat His	tta Leu	ttg Leu	agg Arg 310	tgg Trp	ggg ggg	ttt Phe	ttc Phe	aca Thr 315	cca Pro	gaa Glu	caa Gln	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	Pro	cca Pro 325	ttc Phe	cat His	tgg Trp	Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	Thr	gta Val 340	cat His	cct Pro	ata (Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056

-165-

gtc aat gac ata cag aag tta gtg gga aaa ttr aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Xaa Asn Trp Ala Ser Gln 355 360 365	1104
att tat gca ggg Ile Tyr Ala Gly 370	1116
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ggg caa cta ata gaa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Ile Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
ttg gaa gaa atg aat ttg cca ggg aga tgg aaa cca aaa ata ata ggg Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Ile Ile Gly 35 40 45	144
gga att gga ggt ttt atc aaa gta aga cag tat gat cag ata ccc ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Pro Ile 50 55 60	192
gaa atc tgt gga cat aaa gtt ata rgt cca gta tta ata gga cct aca Glu Ile Cys Gly His Lys Val Ile Xaa Pro Val Leu Ile Gly Pro Thr 65 70 75 80	240
cct gtc aac ata att gga aga aat ttg atg act cag att ggc tgc act Pro Val Asn Ile Ile Gly Arg Asn Leu Met Thr Gln Ile Gly Cys Thr 85 90 95	288
tta aat ttt ccc atc agt cct att raa act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Xaa Thr Val Pro Val Lys Leu Lys 100 105 110	336
cca gga atg gat ggc cca aag gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa gga Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly 130 135 140	432

-166-

aa. Ly: 14!	s Ile	tca Ser	a aaa c Lys	att Ile	999 Gly 150	Pro	gaa Glu	aac Asn	cca Pro	tac Tyr 155	Asr	act Thr	cca Pro	gta Val	ttt Phe 160	480
gco Ala	e ata a Ile	a aag Lys	g aaa E Lys	aaa Lys 165	Asn	agt Ser	act Thr	aga Arg	tgg Trp 170	Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	a gaa g Glu	ctt Lev	aat Asn 180	Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	cct Pro	gga Gly	gly aaa	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	cct Pro	cta Leu	gat Asp 220	gaa Glu	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aat Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
gtt Val	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tcg Ser 255	cca Pro	768
gca Ala	ata Ile	ttt Phe	cag Gln 260	gct Ala	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	ccg Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	cta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	caa Gln	cat His	ttg Leu	ttg Leu	aaa Lys 310	tgg Trp	gga Gly	ttt Phe	atc Ile	aca Thr 315	cca Pro	gat Asp	gaa Glu	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	Met	330 Gly 333	tat Tyr	gaa Glu	ctc Leu	His	cct Pro 335	gat Asp	1008
aag Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aaa Lys :	Leu '	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
	tat Tyr 370		9 9													1115

-167-

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<210> 92
 <211> 1116
 <212> DNA
 <213> Human Immunodificiency Virus (HIV)
<220>
<221> CDS
 <222> (0)...(297)
 <223> HIV Protease
 <221> CDS
 <222> (298) ... (1116)
 <223> Portion of HIV Reverse Transcriptase
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Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly
                                                                                      48
 ggg cag cta aag gaa gct cta tta gat aca gga gca gat gat aca gta
 GIy Gln Leu Lys Glu Ala Leu Leu Asp Thr GIy Ala Asp Asp Thr Val
 tta gaa gac ata aac ttg cca gga aaa tgg aaa cca aaa atg ata ggg
                                                                                    144
Leu Glu Asp Ile Asn Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly
gga att gga ggt ttt atc aaa gta aga cag tat gag cag gta ccc ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Glu Gln Val Pro Ile
                                                                                    192
gaa atc tgt gga cat aaa act ata ggt aca gta tta gta gga cct aca
                                                                                    240
Glu Ile Cys Gly His Lys Thr Ile Gly Thr Val Leu Val Gly Pro Thr
cct gtc aac ata att gga aga aat ctg atg act cag att ggg tgc act
                                                                                    288
Pro Val Asn Ile Ile Gly Arg Asn Leu Met Thr Gln Ile Gly Cys Thr
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
                                                                                    336
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu
                                                                                    384
                                 120
aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa ggg
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly
     130
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt
                                                                                    480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
145
gcc ata aag aaa aag aac agt act aga tgg aga aaa gta gta gat ttc
                                                                                   528
Ala Ile Lys Lys Lys Asn Ser Thr Arg Trp Arg Lys Val Val Asp Phe
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-168-

aga Arg	a gaa g Glu	a ctt 1 Leu	aat Asn 180	Lys	aaa Lys	act Thr	caa Gln	gac Asp 185	Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	Leu	gga Gly	576
ata Ile	e Pro	cat His 195	Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	Lys	aac Asn	aaa Lys	tca Ser	gta Val 205	Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gaa Glu	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	acg Thr	cca Pro	999 Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	ata Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ctg Leu	gtt Val	atc Ile	tgt Cys 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	tta Leu	tat Tyr	gta Val	. 864
gga Gly	tct Ser 290	gac Asp	cta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gaa Glu	gaa Glu	ctg Leu	912
agg Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	gaa Glu	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	ccc Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gac Asp	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
		gca Ala														1116

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-169-

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cct	00> : caç o Gli	g ato	c act e Thi	ctt Lev	tgg Trp	g caa Glr	cga Arg	cco Pro	ato Ile	· Val	aca Thi	a ata Tle	aag Lys	ata Ile	gga Gly	48
G1 ³	g cag Gli	g cta 1 Leu	a aag 1 Lys 20	; Glบ	gct Ala	cta Leu	ata Ile	gat Asp 25	Thr	gga Gly	gca	gat Asp	gat Asp 30	Thr	gta Val	96
tta Leu	gaa Glu	gaa Glu 35	Met	aat Asn	tta Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aca Thr	cca Pro	aaa Lys 45	ata Ile	ata Ile	Gly	144
gga Gly	att Ile 50	Gly	ggt Gly	ttt Phe	gtc Val	aga Arg 55	gta Val	aga Arg	cag Gln	tat Tyr	gaa Glu 60	Gln	ata Ile	ccc Pro	gta Val	192
gaa Glu 65	Ile	tgc Cys	Gly aaa	cat His	aaa Lys 70	gct Ala	gta Val	ggt Gly	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
cct Pro	gcc Ala	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggc Gly	tgt Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gat Asp 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	ara Xaa	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gag Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	ctg Leu 140	gaa Glu	aag Lys	gam Xaa	gga Gly	432
aaa Lys 145	Ile	tca Ser	aaa Lys	Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gct Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	gta Val	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aaa Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	cct Pro	gca Ala	Gly 999	ata Ile	maa Xaa 200	aag Lys	aac Asn	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ytg Xaa	624

-170-

gat gtg Asp Val 210	ggt g Gly i	gat g Asp A	ca tat la Tyr	ttt Phe 215	Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gag Glu	gac Asp	ttc Phe	agg Arg	672
aag tac Lys Tyr 225				Ile										720
att aga Ile Arg	tat o	3ln T	ac aat yr Asn 15	gta Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca ata Ala Ile	Phe G	aa ag Sln Se 260	gt agc er Ser	atg Met	aca Thr	aaa Lys 265	aty Xaa	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aag Lys	816
aaa aat Lys Asn														864
gga tct Gly Ser 290	gac t Asp L	ta ga eu Gl	a ata u Ile	gag Glu 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gat Asp	gaa Glu	ctg Leu	912
aga gac Arg Asp 305	cat c His L	tg tg eu Tr	g aag p Lys 310	tgg Trp	gga Gly	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aac Asn	aaa Lys	yat Xaa 320	960
cag aaa . Gln Lys	gaa c Glu P	ro Pr 32	o Phe	cgt Arg	tgg Trp	atg Met	ggc Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa tgg Lys Trp	Thr V	ta ca al Gl 40	g cct n Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aag Lys	gat Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc aat Val Asn	gac a Asp I 355	ta ca le Gl	g aag n Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
aat tat Asn Tyr 370														1116
<210> 94 <211> 11 <212> DN <213> Hu	A	mmuno	difici	.ency	· Vir	us (HIV)							
<220> <221> CD: <222> (0) <223> HI) (2													
<221> CD: <222> (2: <223> Po:	98)			erse	Tra	nscr	ipta	se						

-171-

CC	00> 9 t cag c Gli	g at	c act	ctt Leu 5	tgg ıTrp	g caa Gln	cga Arg	a ccc g Pro	cto Leu 10	ı Val	aca Thi	a ata	aag Lys	g ata E Ile 15	a ggg e Gly	48
999 G1	g caa y Glr	a cta 1 Lei	a ata 1 Ile 20	Glu	g gct Ala	cta Leu	ttg Leu	gat Asp 25	Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	Thr	gta Val	96
tta Lei	a gaa 1 Glu	gaa Glu 35	ı Met	gat Asp	ttg Leu	cca Pro	gga Gly 40	Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	Ile	ata Ile	gly ggg	144
gga	att Ile 50	: Gly	ggt Gly	tgg Trp	atc Ile	aaa Lys 55	gta Val	aga Arg	caa Gln	tat Tyr	gat Asp 60	Gln	ata Ile	Pro	ata Ile	192
gaa Glu 65	Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gtt Val	ata Ile	agt Ser	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
cca Pro	gtc Val	aac Asn	gta Val	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	atg Met 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aga Arg	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
aag Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	ttg Leu 140	gaa Glu	aag Lys	gat Asp	gjå aaa	432
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
Ala	Ile	Lys	aaa Lys	Lys 165	Asp	Ser	Thr	Lys	Trp 170	Arg	Lys	Val	Val	Asp 175	Phe	528
Arg	GIu	Leu	aat Asn 180	Lys	Arg	Thr	Gln	Asp 185	Phe	Trp	Glu	Val	Gln 190	Leu	Gly	576
TTE	Pro	His 195	Pro	Ala	Gly	Leu	Pro 200	Lys	Lys	Lys	Ser	Val 205	Thr	Val	Leu	624
Asp	Val 210	Gly	gat Asp	Ala	Tyr	Phe :	Ser	Val	Pro	Leu	Asp 220	Glu	Asp	Phe	Arg	672
aaa Lys 225	tat Tyr	act Thr	gca Ala	Phe	acc Thr 230	ata (Ile)	cct Pro	agt : Ser :	Ile :	aat Asn 235	aat Asn	gag Glu	aca Thr	Pro	gga Gly 240	720

-172-

gtt Val	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctc Leu	cca Pro	cag Gln 250	Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	7	68
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	acc Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	Arg	aaa Lys	8	16
cag Gln	aat Asn	cca Pro 275	aac Asn	ata Ile	ctt Leu	att Ile	tgt Cys 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	8	64
gga Gly	Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	gaa Glu 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	9	12
aga Arg 305	caa Gln	cat His	ctg Leu	tgg Trp	aga Arg 310	tgg Trp	Gly 999	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gat Asp	aaa Lys	aaa Lys	cat His 320	9	60
cag Gln	aag Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	100	80
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gag Glu	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	105	56
gtc Val	aat Asn	gat Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agy Xaa	cag Gln	110	04
	tat Tyr 370								·							113	.6
<21:	0> 95 l> 11 2> DN 3> Hu	16 A	Immu	nodi	fici	ency	Vir	us (HIV)								
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<222	l> CD 2> (2 3> Po	98).			Rev	erse	Tra	nscr	ipta	.se							
cct)> 95 cag Gln	atc	act Thr	ctt Leu 5	tgg (Trp (caa Gln .	cga Arg	ccc Pro	ctc Leu 10	gtc Val	aca Thr	ata Ile	aag Lys	ata Ile 15	Gly aaa	4	8
Gly 999	caa Gln	cta (Leu)	aag (Lys (20	gaa Glu	gct (Ala 1	cta Leu :	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	9	6

-173-

tt: Le:	a gaa u Glu	a gaa 1 Glu 35	ı Met	aat Asn	ttg Leu	cca Pro	gga Gly 40	' Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	Met	g ata : Ile	ggg Gly	144
gga Gly	a att 7 Ile 50	Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	Gln	ata Ile	tcc Ser	gta Val	192
gaa Glu 65	ı Ile	tgt Cys	ggr Xaa	cat His	aaa Lys 70	gct Ala	ata Ile	ggt Gly	aca Thr	gta Val 75	Leu	rta Xaa	gga Gly	cct	aca Thr 80	240
cct	gto Val	aac Asn	ata Ile	att Ile 85	gga Gly	agg Arg	aat Asn	ttg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	gga Gly	432
aaa Lys 145	Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aaa Lys	act Thr	caa Gln	gac Asp 185	ttt Phe	tgg Trp	gar Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	Gly 999	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	tac Tyr	act Thr	gca Ala	ttt Phe	act Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
att Ile	aga Arg	tat Tyr	caa Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	Phe	cag Gln 260	tgt Cys	agc Ser	atg Met	Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	Pro	ttt Phe 270	aga Arg	aaa Lys	816

-174-

caa aat cca Gln Asn Pro 275	o Glu Ile	gtt ato Val Ile	tat ca Tyr Gl 280	a tac n Tyr	atg ga Met As _l	t gat p Asp 285	ctg Leu	tat Tyr	gta Val	864
gga tct gac Gly Ser Asp 290	tta gaa Leu Glu	a ata gaa 1 Ile Glu 295	Gln Hi	t aga s Arg	ata aaa Ile Lys 300	s Ile	gag Glu	gaa Glu	ctg Leu	912
aga cac cat Arg His His 305	ctg ttg Leu Leu	aaa tgg Lys Trp 310	gga tt Gly Ph	t wmc e Xaa	aca cca Thr Pro	a gac o Asp	aaa Lys	aaa Lys	cat His 320	960
cag aaa gaa Gln Lys Glu	cct cca Pro Pro 325	Phe Leu	tgg at Trp Me	g ggt t Gly 330	tat gaa Tyr Gli	a ctc a Leu	cat His	cct Pro 335	gat Asp	1008
aaa tgg aca Lys Trp Thr	gta cag Val Gln 340	cct ata Pro Ile	gtg ct Val Le 34	u Pro	gaa aar Glu Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc aat gac Val Asn Asp 355	Ile Gln	aag tta Lys Leu	gtg gg Val Gl 360	a aaa y Lys	tta aat Leu Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
att tac cca Ile Tyr Pro 370										1116
<210> 96 <211> 1116 <212> DNA <213> Human	Immunodi	ificiency	/ Virus	(HIV)						
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<221> CDS <222> (298). <223> Portio			e Transo	ripta	se					
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ggg caa cta Gly Gln Leu	agg gaa Arg Glu 20	gct cta Ala Leu	tta gat Leu Asp 25	Thr	gga gca Gly Ala	gat q Asp 1	gat a Asp 1	aca (Thr	gta Val	96
tta gaa gaa Leu Glu Glu 35	ata aat Ile Asn	ttg cca Leu Pro	gga aga Gly Arg 40	tgg (aaa cca Lys Pro	aaa a Lys N 45	atg a Met I	ata (Gly 999	144
gga att ggg Gly Ile Gly 50	ggt ttt Gly Phe	atc aaa Ile Lys 55	gta aga Val Arg	sag i Xaa i	tat gat Tyr Asp 60	cag g Gln V	gta c /al F	ecc (gta Val	192

-175-

	ı Ile					Ala					. Leu				aca Thr 80		240
Pro	gto Val	aac Asr	ata lle	att Ile 85	Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	Thr	cag Gln	att	ggt Gly	tgc Cys 95	act		288
tta Lei	a aat 1 Asn	ttt Phe	ccc Pro 100	Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	Thr	gta Val	cca Pro	gta Val	ara Xaa 110	tta Leu	aag Lys		336
Pro	ggr Xaa	atg Met 115	Asp	ggc	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	Thr	gaa Glu	gaa Glu		384
aaa Lys	ata Ile 130	Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	atc Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	Gly aaa		432
aaa Lys 145	Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	ata Ile	ttt Phe 160		480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	ggt Gly	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	gta Val	gta Val	gat Asp 175	ttc Phe	!	528
agg Arg	gaa Glu	ctc Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	ggm Xaa	!	576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	ttg Leu	aaa Lys 200	Lys	aaa Lys	aaa Lys	tca Ser	gtr Xaa 205	aca Thr	gta Val	ctg Leu	•	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gaa Glu	gaa Glu	ttc Phe	agg Arg	6	572
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	gta Val	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	7	720
atc Ile	aga Arg	tat Tyr	caa Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aag Lys	gga Gly	tca Ser 255	cca Pro	7	768
gca Ala	ata Ile	ttt Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	ε	316
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtc Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	8	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	9	12

-176-

305	caa c Gln H	at cto is Lev	ttg Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa g Lys G	ag cct lu Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ct c Leu	cat His	cct Pro 335	Asp	1008
aaa (Lys (tgg a Trp T	ca gta nr Val 340	Gln	cgt Arg	ata Ile	gag Glu	ctg Leu 345	cca Pro	gaa Glu	aag Lys	gag Glu	agc Ser 350	tgg Trp	act Thr	1056
gtc a Val 1	aat ga Asn As 35	ac ata sp Ile 55	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	caa Gln	1104
Xaa 1		a ggg o Gly													1116
<212>	> 1116 > DNA	mmI c.	ınodi	.fici	.ency	, Vii	rus ((HIV)			•				
	> CDS > (0).	(29° Protea				_									
	(298)(i		' Rev	erse	Tra	nscr	ipta	ıse						
<400>	97														
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cct c Pro G 1	aa at In Il	c act e Thr a aag e Lys 20	Leu 5 gaa	Trp gcy	Gln tta	Arg tta	Pro gat	Leu 10 aca	gtc Val gga	Lys gca	Ile gat	Lys	Ile 15 aca	Gly	48 96
cct c Pro G 1	aa at aa at aa at	a aag e Lys 20 a atg	Leu 5 gaa Glu aat	Trp gcy Xaa ttg	Gln tta Leu cca	Arg tta Leu	Pro gat Asp 25	Leu 10 aca Thr	gtc Val gga Gly	Lys gca Ala cca	Ile gat Asp	Lys gat Asp 30	Ile 15 aca Thr	gtg Val	
ggg c Gly G tta g Leu G	aa at aa at aa at aa at aa at aa aa at aa aa	a aag e Lys 20 a atg u Met 5	Leu 5 gaa Glu aat Asn	gcy Xaa ttg Leu	tta Leu cca Pro	tta Leu gga Gly 40	gat Asp 25 aaa Lys	Leu 10 aca Thr tgg Trp	gtc Val gga Gly aaa Lys	gca Ala cca Pro	gat Asp aaa Lys 45	Lys gat Asp 30 ttg Leu ata	Ile 15 aca Thr ata Ile	gtg Val ggg Gly	96
ggg c Gly G tta g Leu G	tt gg. tc tg:	a aag e Lys 20 a atg Met 5 a ggt y Gly	gaa Glu aat Asn ttt Phe	Trp gcy Xaa ttg Leu atc	tta Leu cca Pro aaa Lys 55	tta Leu gga Gly 40 gta Val	gat Asp 25 aaa Lys aga Arg	Leu 10 aca Thr tgg Trp cag Gln	gtc Val gga Gly aaa Lys tat Tyr	CCA Pro gat Asp 60	gat Asp aaa Lys 45 Cag Gln	Lys gat Asp 30 ttg Leu ata Ile	Ile 15 aca Thr ata Ile ctt Leu	Gly gtg Val ggg Gly ata Ile	96 144

-177-

tt: Le:	a aa u Asi	t tti n Phe	E CCC Pro	o Ile	agt Ser	cct Pro	att Ile	gaa e Glu 105	Thr	gta Val	a cca l Pro	a gta o Val	a aaa l Lys 110	s Le	a aag u Lys	336
Pro	a gga o Gly	Met	Asp	ggo Gly	cca Pro	aaa Lys	gtt Val	Lys	caa Gln	tgg Trp	cca Pro	tto Lev 125	ı Thi	a gaa c Glu	a gaa ı Glu	384
aaa Lys	a ata 5 Ile 130	: Lys	gca Ala	tta Lev	cta Leu	gaa Glu 135	ıIl∈	tgt Cys	aca Thr	gaa Glu	ctg Lev 140	ı Glu	aag Lys	g gaa Glu	a ggg ı Gly	432
aaa Lys 145	: Ile	tca Ser	aaa Lys	att	999 Gly 150	Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttt Phe	tgg Trp	gag Glu	gtt Val	caa Gln 190	cta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	gsa Xaa	ggg	tta Leu	aga Arg 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	tat Tyr 220	gag Glu	gac Asp	tty Phe	agg Arg	672
aaa Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	act Thr 230	ata Ile	cct Pro	agt Ser	aca Thr	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
att Ile	agg Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	trt Xaa 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	caa Gln	cat His	ctg Leu	tgg Trp	cag Gln 310	tgg Trp	gga Gly	ttt Phe	ttc Phe	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008

WO 01/35316 PCT/US00/30863

-178-

				Gln					Pro					Trp	act Thr	1056
								Gly					Ala		cag Gln	1104
att Ile		_														1116
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<220: <221: <222: <223:	> CD > (0)														
<221: <222: <223:	> (2	98).				verse	e Tra	ansci	ripta	ase		•				
<400; cct (Pro (caa	atc														48
ggg d																96
tta g Leu G																144
gga a Gly I																192
gaa a Glu X 65																240
cct g Pro V																288
tta a Leu A	aat t Asn I	Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca g Pro G	Sly N															384

-179-

aa Ly:	a ata s Ile 130	e Lys	a gca s Ala	tta Lev	a gta ı Val	gaa Glu 135	ı Ile	a tgt e Cys	aca Thr	a gaa Glu	ato Met	: Glu	a aag Lys	g gaa s Glu	a ggg ı Gly	432
aaa Lys 14	s Ile	t tca	a aaa : Lys	att Ile	999 Gly 150	Pro	gaa Glu	a aat 1 Asn	cca Pro	tac Tyr 155	Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gco Ala	ata a Ile	a aag e Lys	aaa Lys	aaa Lys 165	Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa g Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	Pro	gca Ala	gga Gly	tta Leu	aaa Lys 200	Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tat Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gay Asp	ata Ile	gtt Val	att Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tcc Ser 290	gac Asp	cta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	caa Gln	cac His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	ggr Xaa	ttt Phe	acc Thr	ack Xaa 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aag Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gta Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gat Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104

WO 01/35316 PCT/US00/30863

-180-

att tac tca gt Ile Tyr Ser 370	1115
<210> 99 <211> 1115	
<220> <221> CDS <222> (0)(297) <223> HIV Protease	
<221> CDS <222> (298)(1115) <223> Portion of HIV Reverse Transcriptase	
<pre><400> 99 cct cag atc act ctt tgg cag cga ccc ctc gtc aca ata aag ata ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly 1 5 10 15</pre>	48
ggg caa cta aag gaa gct yta tta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Xaa Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gaa atg aat ttg cca gga agr tgg aaa cca aaa atg ata ggg Leu Glu Glu Met Asn Leu Pro Gly Xaa Trp Lys Pro Lys Met Ile Gly 35 40 45	144
gga att gga ggc ttt atc aaa gta aga cag tat gat cag ata ccc cta Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Pro Leu 50 55 60	192
gaa atc tgt ggc cat aag gct ata ggt aca gta tta gta gga cct aca Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr 65 70 75 80	240
cct gtc aac ata att gga aga aat ctg ttg act cag att ggt tgc act Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr 85 90 95	288
tta aat ttt ccc att agt cct att gaa act gta cct gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336
cca gga atg gat ggt cca aaa gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta gta gaa att tgt aca gag atg gaa aag gaa ggg Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly 130 135 140	432
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe 145 150 155 160	480

-181-

				•													•	
	gc Ala	c ata a Ile	a aag e Lys	g aaa s Lys	a aaa E Lys 165	Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170) Arg	aaa , Lys	tta Leu	a gta 1 Val	gat Asp 175	ttc Phe	528	
	aga Arg	a gaa g Glu	a cti 1 Lei	aat 1 Asn 180	Lys	aga Arg	act Thr	caa Gln	gac Asp 185	Phe	tgg Trp	gaa Glu	gtt Val	Caa Gln 190	Let	gga Gly	576	
	ata Ile	e Pro	cat His	ccc Pro	tca Ser	999 999	tta Leu	raa Xaa 200	aag Lys	aag Lys	aaa Lys	tca Ser	gta Val 205	Thr	gta Val	ctg Leu	624	
	gat Asp	gtg Val 210	. GIY	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	cca Pro	gat Asp	ttc Phe	agg Arg	672	
	aag Lys 225	Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720	
	att Ile	agg Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768	
	gca Ala	ata Ile	ttc Phe	caa Gln 260	agc Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816	
	caa Gln	aat Asn	cca Pro 275	gaa Glu	ata Ile	gtt Val	atc Ile	tac Tyr 280	caa Gln	tac Tyr	dtg Xaa	gat Asp	gat Asp 285	ttg Leu	tak Xaa	gta Val	864	
	rgc Xaa	tct Ser 290	gac Asp	tta Leu	gaa Glu	Ile	999 Gly 295	cag Gln	cat His	aga Arg	gca Ala	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912	
	aga Arg 305	caa Gln	cat His	ctg Leu	Leu	agg Arg 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aag Lys	cat His 320	960	
	cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008	
	aaa Lys	tgg Trp	aca Thr	gtt Val 340	cag Gln	cct Pro	ata (Ile	Val	ctg Leu 345	cca Pro	gaa Glu	aag Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056	
•	gtc Val	aat Asn	gac Asp 355	ata Ile	cag a Gln :	aag (Lys)	Leu '	gtg Val 360	gga Gly	aaa Lys	ttg Leu .	Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104	
	Ile	tat Tyr 370	gca Ala	9 9													1115	

<210> 100 <211> 1115 -182-

	12> 1 13> 1		ı Im	nunoc	lific	cienc	y Vi	.rus	(HIV	7)						
<22 <22	20> 21> (22> 23> F	(0).					-									
<22	21> (22> (23> E	(298)				vers	e Tr	ansc	ript	ase						
cct	00> 1 caa Glr	ato	act Thr	ctt Leu 5	tgg Trp	caa Gln	cga Arg	ccc Pro	cta Leu 10	Val	aca Thr	ata Ile	aag Lys	ata Ile 15	gga Gly	48
ggg Gly	cag Gln	ctr Xaa	aag Lys 20	Glu	gct Ala	ata Ile	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	Thr	kta Xaa	96
tta Leu	gaa Glu	gaa Glu 35	Met	aat Asn	tng Xaa	ccc Pro	gga Gly 40	aga Arg	tgg Trp	ama Xaa	cca Pro	ama Xaa 45	ttg Leu	ata Ile	Gly aaa	144
gga Gly	att Ile 50	Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	cag Gln	ata Ile	ccc Pro	ata Ile	192
gaa Glu 65	atc Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gtt Val	ata Ile	ggt Gly	aca Thr	gta Val 75	ttg Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
cct Pro	acc Thr	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	atg Met 90	act Thr	cag Gln	ctt Leu	ggt Gly	tgc Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	ttg Leu 140	gaa Glu	aag Lys	gaa Glu	ej aaa	432
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576

-183-

ata c Ile F	cca Pro	cat His 195	ccc Pro	gca Ala	Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	ata Ile	ctg Leu	624
gat g Asp V	gtg Zal	ggc Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
aaa g Lys V 225																720
att a Ile A																768
gca a Ala I																816
caa a Gln A	sn															864
gga to Gly So 2:																912
aga ca Arg G 305																960
cag as Gln Ly			Pro													1008
aaa to Lys Ti		Thr														1056
gtc aa Val As	sn :					Leu										1104
att to Ile Xa			aa													1115
<210><211><211><212><213>	109 DN2	96 A	Immu	nodi	fici	ency	Vir	us (HIV)							
<220><221><222><223>	(0)															

-184-

<2		(298		(1096 of H)		evers	se Tı	canso	cript	ase						
CC	00> t ca o Gl:	r at	c act	t ctt r Leu 5	tgg Trp	g cag Glr	aco Thr	e ccc	ctt Leu	ı Val	yca Xaa	a ata	a agg e Arg	g aka g Xaa 15	a ggg a Gly	48
gg: Xaa	r cag a Gli	g yta n Xaa	a aag a Lys 20	s Glu	gct Ala	tta Leu	tta Leu	gay Asp 25	Thr	gra Xaa	gca Ala	gat Asp	gat Asp 30	Xaa	gta Val	96
tta Lei	a gaa 1 Glu	a gaa 1 Glu 35	ı Met	tat Tyr	ttg Leu	cca Pro	gga Gly 40	Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	Met	ata Ile	Gly Gly	144
gga Gly	att 7 Ile 50	: GIŽ	a ggt / Gly	ttt Phe	atc Ile	aag Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	Gln	ata Ile	ccc	ata Ile	192
gaa Glu 65	ITE	tgt Cys	gga Gly	cac His	aaa Lys 70	Ala	ata Ile	ggt Gly	aca Thr	gta Val 75	ttg Leu	gta Val	gga Gly	tct Ser	aca Thr 80	240
cct	gtt Val	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	acc Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	tct Ser	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aga Arg 110	tta Leu	aag Lys	336
ccc Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aag Lys	caa Gln	tgg Trp	cca Pro	tta Leu 125	aca Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	Gly 999	432
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aag Lys 165	aac Asn	agt Ser	gat Asp	aga Arg	tgg Trp 170	aga Arg	aaa Lys	gta Val	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	acc Thr	Gln	gac Asp 185	ttt Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	999 Gly	Leu	aaa Lys 200	agg Arg	aga Arg	aaa Lys	Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	Tyr	ttt Phe 215	tca Ser	att Ile	ccc Pro	Leu	gat Asp 220	aaa Lys	gaa Glu	ttc Phe	aga Arg	672

-185-

	g tat s Tyr															720	
	aga Arg															768	
	ata														gaa Glu	816	
cag Gln	aat Asn	cca Pro 275	gac Asp	atg Met	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864	
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	gca Ala	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912	
	caa Gln															960	
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	ccg Pro 335	gat Asp	1008	
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	act Thr	ata Ile	gtg Val	ctg Leu 345	cca Pro	gag Glu	aag Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056	
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gta Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	g			1096	
<212	0> 10 L> 10 2> DN 3> Hu	48 A	Immu	nodi	fici	ency	Vir	us (HIV)								
<222)> L> CD !> (0 !> HI)	-	-													
<222	.> CD !> (2 !> Po	98).	(1 n of	048) HIV	Rev	erse	Tra	nscr	ipta	se							
cct	> 10 cag Gln	atc	act (ctt Leu '	tgg Trp	cag Gln .	cga Arg	ccc Pro	tty Phe 10	gtc Val	aca Thr	ata Ile	aag Lys	gta Val 15	Gly 999	48	
Gly aaa	caa Gln :	cta (Leu)	aag g Lys (20	gaa g Glu i	gct (Ala 1	cta Leu :	ttg (Leu)	gat Asp 25	aca Thr	gga (Gly)	gca Ala	gat (Asp .	gat Asp 30	aca Thr	ata Ile	96	

-186-

tt Le	a ga u Gl	a gaa u Gli 3!	u Met	g tgi	t ttg s Lei	g cca ı Pro	gga Gly	Arg	tgg Trp	g aaa Dys	a cca s Pro	a aaa b Lys 49	Le	g ata	a ggg e Gly		.44
G1	a at y Ilo 50	e Gly	a ggt y Gly	ttt Phe	gto Val	aaa Lys 55	Val	aga Arg	caa Glr	tat Tyr	gat Asp 60	Glr	g ata n Ile	e Pro	ata Ile	1	92
ga: Gl: 6!	u Ile	c tgt e Cys	gga Gly	cat His	aaa Lys 70	: Val	ata Ile	ggt Gly	aca Thr	gta Val 75	. Leu	gta Val	gga Gly	cct Pro	aca Thr 80	2	40
Pro	gco Ala	a ac a Asr	ata Ile	gtt Val 85	. Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	Thr	cag Gln	att	ggc	tgt Cys 95	act Thr	2	88
tta Lei	a aat 1 Asr	ttt Phe	Pro	Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	Leu	aag Lys	33	36
cca Pro	a gga o Gly	atg Met 115	Asp	gly aaa	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	38	34
aaa Lys	ata Ile 130	Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att	tgt Cys	aca Thr	gaa Glu	ttg Leu 140	gag Glu	aag Lys	gat Asp	gga Gly	43	32
aaa Lys 145	Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tay Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	48	30
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	aat Asn	agt Ser	gat Asp	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	gta Val	gta Val	gat Asp 175	ttc Phe	52	8
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtc Val	caa Gln 190	tta Leu	gga Gly	57	6
ata Ile	cca Pro	cat His 195	ccc Pro	gga Gly	gly aaa	tta Leu	rag Xaa 200	aag Lys	aac Asn	aaa Lys	tca Ser	ata Ile 205	aca Thr	gta Val	ctg Leu	62	4
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	att Ile	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	aga Arg	67	2
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	ccy Xaa	agt Ser	Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	72	0
att Ile	aga Arg	tat Tyr	cag Gln	tat Tyr 245	aat Asn	gtg Val	ctt Leu	Pro	cag Gln 250	gga Gly	tgg Trp	aag Lys	gga Gly	tca Ser 255	cca Pro	76	8
gcc Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	Thr	aaa Lys 265	ata Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aag Lys	816	6

-187-

ca: Gl:	a aa n As:	t cca n Pro 275) Asp	ata Ile	a ati	t ato e Ile	gtt Val	l Glr	tac Tyr	gtg Val	g gat L Asp	gat Asp 285) Le	g ta 1 Ty:	t gta r Val	864
gca Ala	a tc: a Se: 290	r Asp	tta Lev	gaa Glu	a ata 1 Ile	a ggg e Gly 295	Glr	g cat His	aga Arg	aca Thr	aaa Lys 300	: Il ϵ	a aag	g gaa s Glu	a cta ı Leu	912
aga Arg 305	g Glı	a tat n Tyr	ctg Leu	tgg Tr	gag Glu 310	ı Trp	gga Gly	ttt Phe	tac Tyr	aca Thr 315	Pro	gac Asp	aaa Lys	a aaa E Lys	cat His 320	960
caa Glr	a cag n Glr	g gaa n Glu	ccc Pro	Pro 325	Phe	ctc Leu	tgg Trp	atg Met	999 330	Tyr	gag Glu	Leu	cat His	cct Pro	gat Asp	1008
aaa Lys	tgg Trp	g aca Thr	gta Val 340	Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	a			1048
<21 <21	0> 1 1> 1 2> D 3> H	116 NA	Imm	unod	ific	ienc	y Vi:	rus	(HIV))						
<22	1> C 2> (DS 0) IV P														
<22	1> C 2> (3> P	298)	(: on of	L116) V Re	verse	e Tra	ansci	ripta	ıse						
cct	0> 1 cag Gln	atc	act Thr	ctt Leu 5	tgg Trp	caa Gln	cga Arg	ccc Pro	ctc Leu 10	gtc Val	aca Thr	ata Ile	arg Xaa	rta Xaa 15	gjy aaa	48
Gly 999	cag Gln	cta Leu	aag Lys 20	gaa Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
tta Leu	gaa Glu	gaa Glu 35	atg Met	aat Asn	ttg Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	gly aaa	144
gga Gly	att Ile 50	gga Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	cag Gln	Ile	Pro	ata Ile	192
Gly gaa	50 atc	Gly	Gly gga	Phe cat	Ile	Lys	Val gaa	Arg ggt	Gln aca	Tyr qta	Asp 60 tta	Gln	Ile	Pro	Ile aca	192 240

-188-

tta Lei	a aat 1 Asr	ttt Phe	Pro) Ile	agt Ser	cct	att Ile	gaa Glu 105	Thr	gta Val	cca Pro	gta Val	a aaa L Lys 110	: Lei	a aag 1 Lys	336
Pro	gga Gly	atg Met 115	Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	. Lys	Caa Gln	tgg Trp	cca Pro	Lev 125	Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	Lys	gca Ala	tta Leu	aba Xaa	gaa Glu 135	Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	Glu	aag Lys	gaa Glu	ggr Xaa	432
aaa Lys 145	Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	Asn	act Thr	ccg Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aaa Lys	act Thr	caa Gln	gac Asp 185	ttt Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cac His 195	ccc Pro	gca Ala	Gly aaa	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gaa Glu	ttc Phe	agg Arg	672
aag Lys 225	tat Tyr	aca Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	aca Thr	aac Asn 235	aat Asn	gag Glu	aca Thr	ccc Pro	agg Arg 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tcg Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	Ile	gtt Val	Ile	Tyr	Gln	Tyr	Val	Asp	gat Asp 285	Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gag Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	saa Xaa	cat His	ctg Leu	ttg Leu	agg Arg 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008

-189-

aaa Lys	a tg s Tr	g ac. p Th:	a gt: r Xaa 340	a Gl	g cc	t ata	a raq	g ctg a Lem 34!	u Pro	a gaa o Glu	a aaa 1 Ly:	a gad s Asi	s ag Se: 35	r Tr	g act p Thr	1056
gto Val	c aa l Asi	t gad n Ası 35!	p Ile	a caq e Gli	g aaa n Lys	a tta s Lei	gto Val 360	l Gly	a aaa / Lys	a tta s Lev	a aat 1 Asi	tgg Trp 365	Ala	a agi	t cag r Gln	1104
		r Āla	a gga a Gly													1116
<21 <21	.0> 1 .1> 1 .2> I	1116 DNA	ı Imm	unod	lific	:ienc	y Vi	.rus	(HIV	')						
<22	1 > C 2 > (0)	.(29 Tote													
<22	1> C 2> (3> P	298)	(on o	1116 f HI) V Re	vers	e Tr	ansc	ript	ase						·
cct	0> 1 cag Gln	atc	act Thr	ctt Leu 5	tgg Trp	caa Gln	cga Arg	ccc Pro	mty Xaa 10	gtc Val	aca Thr	ata Ile	aag Lys	gta Val 15	Gly	48
Gly aaa	caa Gln	tta Leu	aaa Lys 20	gaa Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
cta Leu	gaa Glu	gaa Glu 35	ata Ile	aat Asn	ttg Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	gly aaa	144
gga Gly	att Ile 50	gga Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	car Gln	ata Ile	cyt Xaa	ata Ile	192
gaa Glu 65	atc Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gct Ala	ata Ile	ggt Gly	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
cct Pro	gtc Val	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttr Xaa 90	act Thr	cag Gln	att Ile	ggc Gly	tgc Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	ata Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384

-190-

aa: Ly:	a at s Il	е Ly	a gca s Ala	a tta a Lei	a gya ı Xaa	gaa Glu 135	ı Ile	t tg:	t aca	a gaa r Gli	a ato u Met 140	: Glı	a aaq ı Lys	g gaa	a gga u Gly	432
aaa Ly: _14!	s II	t tca	a aaa c Lys	a att	ggg Gly 150	Pro	gaa Glu	a aat ı Ası	cca n Pro	tac Type 155	r Asr	act Thr	cca Pro	a gta	a ttt l Phe 160	480
gct Ala	ata a Ile	a aag e Lys	g aaa Lys	aaa Lys 165	: Asp	agt Ser	act Thi	aaa Lys	tgg Trp	Arç	a aas J Lys	tta Lev	gta Val	gat Ası 175	ttc Phe	528
aga Arg	a gaa g Glu	t Ctt	aat Asn 180	Lys	aga Arg	act Thr	Caa Glr	gac Asp 185	Phe	tgg Trp	gaa Glu	gtt Val	Caa Gln 190	Let	a gga a Gly	576
ata Ile	cca Pro	cat His 195	Pro	gca Ala	ggg Gly	cta Leu	CCa Pro 200	Arg	aaa Lys	aga Arg	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	cca Pro	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	ccg Pro	999 Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gta Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gcc Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	att Ile	tta Leu	gat Asp	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	att Ile	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gca Ala	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cac His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gaa Glu	gaa Glu	cta Leu	912
aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	agg Arg 310	tgg Trp	gga Gly	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttt Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys :	Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104

-191-

		r Al	ca gg la Gl				-						,				1116
<2 <2	12>	1116 DNA	n Im	muno	difi	cien	cy V	irus	(HI	V)							
<2 <2		(0).	(2: Prote						*								
<2: <2:	23> 1	(298 Port) ion d	(1116 of H	5) IV Re	evers	se Ti	ranso	crip	tase							
cct	00> : cag o Gli	ato	c act	ctt Lev	tgg Tr	g caa Glr	a cga a Arc	e cco	tto Phe	≥ Val	gto Val	gta L Val	aag Lys	g ata ; Ile 15	e Gly		48
G1?	g caa g Glr	a cta 1 Lei	a aag 1 Lys 20	GIU	gct Ala	cta Leu	tta Leu	gat Asp 25	Thr	gga Gly	gca Ala	gat Asp	aat Asn 30	Thr	gta Val	~	96
ttt Phe	gaa Glu	gac Asp 35	лаа	aat Asn	ttg Leu	cca Pro	gga Gly 40	Lys	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	Met	ata Ile	ggg Gly		144
gga Gly	att Ile 50	GIY	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	vai	aga Arg	cag Gln	tat Tyr	gat Asp 60	Gln	gta Val	ctt Leu	gta Val		192
gaa Glu 65	116	tgt Cys	gga Gly	caa Gln	aaa Lys 70	gct Ala	ata Ile	ggt Gly	aca Thr	gta Val 75	tta Leu	ata Ile	gga Gly	cct Pro	aca Thr 80		240
cct Pro	gtc Val	aac Asn	ata Ile	att Ile 85	gga Gly	agg Arg	gat Asp	ctg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr		288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys		336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu		384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	Gly aaa		432
aar Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aac Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160		480

-192-

gc Al	c at a Il	a aa .e Ly	ag aa Ys Ly	aa aa /s Ly 16	o no	c ag p Se	t ac r Th	t aa: r Ly:	r tg s Tr	p Ar	a aa g Ly	a tt s Le	a gt u Va	a ga 1 As	t tto p Phe	528
ag Ar	a ga g Gl	a ct u Le	t aa eu As 18	עם זוי	g ag s Ar	a act g Th:	t caa r Gli	a gad n Ası 189	o Phe	c tgg e Trp	g ga o Gl	a gt u Va	t ca l Gl 19	n Le	a gga u Gly	576
at Il	a cc e Pr	a ca o Hi 19	S FI	t gc o Al	a ggg a Gl	g tta y Lei	a aaa 1 Lys 200	з гля	g aaa E Lys	a aaa s Lys	tca Sea	a gta r Val 205	l Th	a gt r Va	a ctg l Leu	624
ga Asj	t gt P Va 21		t ga y As	t gca p Ala	a tat a Tyr	ttt Phe 215	: Sei	gtt Val	Pro	tta Leu	gat Asr 220	Glu	a gay ı Ası	y tto Pho	c agg e Arg	672
aag Lys 225		t ac r Th	t gca r Ala	a ttt a Phe	acc Thr 230	. тте	cct Pro	agc Ser	ata Ile	aac Asn 235	Asn	gag Glu	aca Thi	cca Pro	a gga o Gly 240	720
att Ile	aga Arg	tai Ty:	t cag r Glr	tac Tyr 245	ASI	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	tto Phe	caa Glr 260	L Cys	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gat Asp	cct Pro	ttt Phe 270	Arg	aag Lys	816
Gln	aat Asn	Pro 275	, wer	cta Leu	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	rtg Xaa	gat Asp	gac Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gat Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	car Gln	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aar Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	Mec	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	vaı	ctg Leu 345	cca Pro	gaa Glu	aag Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga (Gly :	aaa Lys :	ttg : Leu :	Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
att Ile	tac Tyr 370	cca Pro	ggg Gly													1116

<210> 106 <211> 1116 -193-

	12> 13>		ın Im	muno	difi	ciend	⊃y V:	irus	(HI	V)						
<2 <2		(0).	(2 Prot													
<2		(298		(1116 of H		evers	e Tr	ansc	ript	ase						
cct	00> ; caç cGli	gat	c act	t ctt Let 5	ngg Xaa	g caa Gln	cga Arg	ccπ Xaa	att Ile	· Val	e aca	a ata r Ila	a aag E Lys	g gta s Val	ggg Gly	48
G17 333	g car ⁄Xaa	n tta a Lei	a aaa 1 Lys 20	s Glu	gtt Val	ytt Xaa	tta Leu	gat Asp 25	Xaa	gga Gly	gca Ala	gat Asp	gat Asp 30	Xaa	gta Val	96
tta Leu	gaa Glu	a gaa a Glu 35	ı Xaa	gat Asp	ttg Leu	cca Pro	gga Gly 40	Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	Met	ata Ile	Gly	144
gga Gly	att Ile 50	; GT	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	Gln	ata Ile	gtt Val	gta Val	192
65	TTE	: Cys	: GIY	His	Lys 70	gct Ala	Ile	Gly	Thr	Val 75	Leu	Val	Gly	Pro	Thr 80	240
cct Pro	gtc Val	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	ctt Leu	ggt Gly	tgc Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gag Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	ttg Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	gga Gly	432
aaa Lys 145	att Ile	tca Ser	aaa Lys	aty Xaa	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
AIA	TTE	гуs	гуз	Lys 165	Asp	agt Ser	Thr	Lys	Trp 170	Arg	Lys	Leu	Val	Asp 175	Phe	528
agg Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576

-194-

ata Ile	e Pro	a ca D Hi 19	S LIC	c gca o Ala	a ggg	g yta / Xaa	a aaa a Lys 200	s rila	g aad S Asi	c aaa n Lys	a tc. s Se:	a gta r Val 209	l Th	a gt r Va	a ctg l Leu	624
gat Asp	gtg Val		t gat Y Asp	gca Ala	tat Tyr	tto Phe 215	: ser	a gtt Val	ccc. Pro	tta Lei	a gat 1 Asp 220	o Lys	a gad s Asp	c tt o Ph	t agg e Arg	672
225	-1-		. Ald	· FIIC	230	116	PIC	ser	TIE	235	Asr	ı Glu	Thr	Pro	ggg Gly 240	720
att Iļe	aga Arg	tat Tyr	cag Gln	tat Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	caa Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	cta Leu	gag Glu	cct Pro	ttt Phe 270	agg Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gaa Glu	gaa Glu	ctg Leu	912
aga Arg 305	gca Ala	cat His	ctg Leu	tta Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gay Asp	aaa Lys	aag Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttt Phe	ctt Leu	tgg Trp	met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa (Lys :	tgg Trp		gtg Val 340	cag Gln	cct . Pro	ata Ile :	Lys	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc a		gat Asp 355	ata (cag : Gln :	aag (Lys)	Leu	gtg Val 360	gga (Gly :	aaa Lys	ttg Leu .	Asn	tgg Trp 2 365	gcc Ala	agt Ser	cag Gln	1104
att t Ile 1 3	at (yr 1 70	cca Pro	gga Gly													1116
<210><211><211><212><213>	111	L6 A	Immur	odif	icie	ncy	Viru	ıs (H	IIV)				-			
<220> <221> <222> <223>	CDS (0)	; ((297)													

-195-

<221> CDS <222> (298)(1116) <223> Portion of HIV Reverse Transcriptase	
<pre><400> 107 cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag ata Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile 1 5 10 15</pre>	ggg 48 Gly
ggg caa cta aag gaa gct tta tta gat aca gga gca gat gat aca Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr 20 25 30	gta 96 Val
tta gaa gaa atg gaa ttg cca gga aga tgg aaa cca aaa atg ata Leu Glu Glu Met Glu Leu Pro Gly Arg Trp Lys Pro Lys Met Ile 35 40 45	999 144 Gly
gga att gga ggt ttt atc aaa gta agm cag tat gat cag ata ccc Gly Ile Gly Gly Phe Ile Lys Val Xaa Gln Tyr Asp Gln Ile Pro 50 55 60	ata 192 Ile
gaa att tgt gga cat aaa gct gtg ggt aca gta tta gta gga cct Glu Ile Cys Gly His Lys Ala Val Gly Thr Val Leu Val Gly Pro 65 70 75	aca 240 Thr 80
cct gtc aac ata att gga aga aat ctg ttg act aag att ggt tgc ? Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Lys Ile Gly Cys : 85 90 95	act 288 Thr
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta a Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu I 100 105 110	aag 336 Lys
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa g Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu G 115 120 125	gaa 384 Slu
aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa g Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu G 130 135	iga 432 :ly
aaa att toa aaa att gga oot gaa aat ooa tao aat act ooa gta t Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val P 145 150 155 1	tt 480 he 60
gcc ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat t Ala Ile Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp P 165 170 175	tc 528 he
aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtt caa tta g Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu G 180 185 190	ga 576 ly
ata cca cat ccc gca ggg tta aaa mgg aaa aaa tca gta aca gta ct Ile Pro His Pro Ala Gly Leu Lys Xaa Lys Lys Ser Val Thr Val Le 195 200 205	eg 624 eu
gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aaa gag ttc ag Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Glu Phe Ar 210 215 220	gg 672 eg

-196-

	Sly 140
att aga tat cag tac aat gtg yyt cca cag gga tgg aaa gga tca c Ile Arg Tyr Gln Tyr Asn Val Xaa Pro Gln Gly Trp Lys Gly Ser P 245 250 255	ro
gca ata ttc caa agt agc atg aca aaa atc tta gag cct ttt aga a Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg L 260 265 270	ys
caa aat cca gaa ata gtt atc tat cag tac atg gat gat ttg tat gt Gln Asn Pro Glu Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Va 275 280 285	al
gga tct gac tta gaa ata ggg cag cac aga aca aaa ata gag gaa ct Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Le 290 295 300	g 912 eu
aga caa cat ctg ttg aag tgg gga ttt acc aca cca gac aaa aaa ca Arg Gln His Leu Leu Lys Trp Gly Phe Thr Thr Pro Asp Lys Lys Hi 305 310 315	.s 0
cag aaa gaa ccc cca ttc ctt tgg atg ggt tat gaa ctc cat cct ga Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro As 325 330 335	p
aaa tgg aca gta cag cct ata gtg cta cca gaa aaa gac agc tgg ac Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Th 340 345 350	r
gtc aat gac ata cag aag tta gtg gga aaa tta aat tgg gcg agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gli 355 360 365	g 1104 n
att tay gca ggg Ile Tyr Ala Gly 370	1116
<210> 108 <211> 1116 <212> DNA <213> Human Immunodificiency Virus (HIV)	
<220> <221> CDS <222> (0)(297) <223> HIV Protease	
<221> CDS <222> (298)(1116) <223> Portion of HIV Reverse Transcriptase	
<pre><400> 108 cct caa atc act ctt tgg caa cga ccc ctc gtc aca ata aag ata ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly 1 5 10 15</pre>	48

-197-

ggg cag cta aag gaa gct cta tta gat aca gga gca gat gat aca gtg Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gaa atg aat ttg cca ggg aaa tgg aag cca aaa atg ata ggg Leu Glu Glu Met Asn Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly 35 40 45	144
gga att gga ggg ttt atc aaa gta agm crg tat gat cag ata ccc ata Gly Ile Gly Gly Phe Ile Lys Val Xaa Xaa Tyr Asp Gln Ile Pro Ile 50 55 60	192
gaa atc tgt gra cat aaa gct aya ggt aca gta tta ata ggm cct act Glu Ile Cys Xaa His Lys Ala Xaa Gly Thr Val Leu Ile Xaa Pro Thr 65 70 75 80	240
cct gtc aac ata att gga aga awt ctg atg act cag att ggg tgc act Pro Val Asn Ile Ile Gly Arg Xaa Leu Met Thr Gln Ile Gly Cys Thr 85 90 95	288
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gag Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa ggg Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly 130 140	432
aag att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe 145 150 155 160	480
gct ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe 165 170 175	528
aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtt caa tta gga Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly 180 185 190	576
ata cca cat cct gca ggt tta aaa aag aaa aaa tca gta aca gta cta Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu 195 200 205	624
gat gtg ggg gat gca tat ttt tca gtt ccc tta gat gaa aac ttc agg Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asn Phe Arg 210 220	672
aag tat act gca ttt acc ata cct agt ata aac aat gag aca cca ggg Lys Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly 235 240	720
att aga tat cag tac aat gta ctt cca cag gga tgg aaa gga tca cca Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro 245 250 255	768

-198-

gca Ala	a ata a Ile	ttc Phe	caa Gln 260	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys 265	Ile	tta Leu	gag Glu	cct Pro	ttc Phe 270	Arg	aag Lys	816
caa Glr	a aat 1 Asn	cca Pro 275	gaa Glu	atg Met	gtt Val	atc Ile	trc Xaa 280	Gln	tac Tyr	gtg Val	gat Asp	gay Asp 285	ttg Leu	tat Tyr	gta Val	864
ggt Gly	Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	gca Ala	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctr Xaa	912
aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	agg Arg 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctm Xaa	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gtg Val 340	cag Gln	cat His	ata Ile	gaa Glu	ctg Leu 345	cca Pro	gaa Glu	caa Gln	gag Glu	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	yta Xaa	aat Asn	tgg Trp 365	gca Ala	agy Xaa	cag Gln	1104
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cct	> 10: caa a Gln :	atc a	ct c	tt t eu 1	rp (caa d Gln <i>l</i>	ega (Arg)	ecc a Pro :	atc q Ile V	gtc a Val 1	aca q Thr '	gta a Val I	aag a Lys 1	ata q [le (gag Slu	48
GJA (cag (Gln I	cta a Leu I	ag g ys G 20	aa g lu <i>P</i>	gct y Ala X	rta t Kaa I	ta g Leu <i>l</i>	gat a Asp 1 25	aca c	gga g Sly A	gca g Ala <i>l</i>	gat a Asp A	at a sn 1	aca o	yta Val	96
ttg d	gam g Kaa G	gaa a Slu I 35	ta a le A	at t sn I	tg c eu P	ca g	ga a lly A 40	iga t lrg 1	gg a	aa c ys F	ca a Pro I	aa a ys M 45	itg a let I	ita e le 6	jly 199	144

-199-

gga Gly	a att / Ile 50	: Xaa	ggt Gly	ttt Phe	ato Ile	aaa Lys 55	gta Val	aam Xaa	cag Gln	tat Tyr	gat Asp 60	Xaa	ata Ile	mcc Xaa	ata Ile	192
	Ile					Val					Leu				aca Thr 80	240
cct	gtc Val	aac Asn	ata Ile	att Ile 85	Gly	aga Arg	gat Asp	ctg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggc Gly	tgc Cys 95	act	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gar Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	ttg Leu 140	gaa Glu	aag Lys	gaa Glu	gga Gly	432
aag Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aac Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aag Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	cct Pro	gca Ala	gly aaa	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	tty Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gmt Xaa 220	aaa Lys	gaa Glu	tnn Xaa	nnn Xaa	672
nnn Xaa 225	nnn Xaa	nnn Xaa	nnn Xaa	nnn Xaa	nnn Xaa 230	nnn Xaa	nnn Xaa	nnn Xaa	nnn Xaa	nnn Xaa 235	nnn Xaa	nnn Xaa	nnn Xaa	nnn Xaa	nnn Xaa 240	720
nnn Xaa	nnn Xaa	nnn Xaa	Xaa	nnn Xaa 245	nnn Xaa	nnn Xaa	nnn Xaa	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gaa Glu	ata Ile	gtt Val	Ile	tac Tyr 280	car Gln	tac Tyr	rtg Xaa	qaA	gay Asp 285	ttg Leu	ttw Xaa	gta Val	864

WO 01/35316 PCT/US00/30863

-200-

Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu 290 295 300	912
aga caa cat ctg ttg agg tgg gga ttt acc aca cca gac aaa aaa cat Arg Gln His Leu Leu Arg Trp Gly Phe Thr Thr Pro Asp Lys Lys His 305 310 315 320	
cag aaa gaa cct cca ttc ctt tgg atg ggy tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Xaa Tyr Glu Leu His Pro Asp 325 330 335	
aaa tgg aca gta cag cct ata gtg ctg cca gaa aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350	
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	
att tat cca ggg Ile Tyr Pro Gly 370	1116
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<220>	
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<222> (0)(297)	· .
<pre><222> (0)(297) <223> HIV Protease <221> CDS <222> (298)(1116)</pre>	48
<pre><222> (0)(297) <223> HIV Protease <221> CDS <222> (298)(1116) <223> Portion of HIV Reverse Transcriptase <400> 110 cyt cag atc act ctt tgg caa cga ccc cts gtc aca ata aag gta ggg Xaa Gln Ile Thr Leu Trp Gln Arg Pro Xaa Val Thr Ile Lys Val Gly</pre>	48 96
<pre><222> (0)(297) <223> HIV Protease <221> CDS <222> (298)(1116) <223> Portion of HIV Reverse Transcriptase <400> 110 cyt cag atc act ctt tgg caa cga ccc cts gtc aca ata aag gta ggg Xaa Gln Ile Thr Leu Trp Gln Arg Pro Xaa Val Thr Ile Lys Val Gly 1</pre>	
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-201-

					_					Thr					act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
					cca Pro											384
		Lys			ata Ile											432
aaa Lys 145	Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
					gac Asp											528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
					Gly ggg											624
					tat Tyr											672
					mcc Xaa 230											720
					aat Asn											768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	mat Xaa	cca Pro 275	gac Asp	atg Met	gty Xaa	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	ggr Xaa 295	cag Gln	cat His	aga Arg	gca Ala	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	cag Gln	cat His	ttg Leu	ttg Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aag Lys	cat His 320	960

WO 01/35316 PCT/US00/30863

-202-

				cca Pro 325											gat Asp	1008
				cag Gln												1056
				cag Gln												1104
	tac Tyr 370	Pro														1116
<21 <21	0 > 1: 1 > 1: 2 > D: 3 > H:	116 NA	Immı	ınodi	fici	ency	/ Vii	rus :	(HIV)	•						
<22	1> Cl 2> (0)	. (297 rotea													
<22		298)		1116) HIV		rerse	e Tra	ınscı	ripta	ıse						
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		atc		ctt Leu 5												48
Pro 1 ggg	Gln	atc Ile ata	Thr	Leu	Trp	Gln	Arg	Pro gat	Leu 10 aca	Val gga	Thr	Ile gat	Lys	Ile 15 aca	Gly	48 96
Pro 1 ggg Gly	Gln caa Gln gaa	atc Ile ata Ile	Thr aag Lys 20 atg	Leu 5 gaa	Trp gct Ala ttg	Cta Leu Cca	Arg tta Leu gga	Pro gat Asp 25	Leu 10 aca Thr	Val gga Gly aaa	Thr gca Ala cca	Ile gat Asp	Lys gat Asp 30 atg	Ile 15 aca Thr	gta Val	
Pro 1 ggg Gly tta Leu	Gln caa Gln gaa Glu att	atc Ile ata Ile gaa Glu 35	Thr aag Lys 20 atg Met	Leu 5 gaa Glu agc	gct Ala ttg Leu	Gln cta Leu cca Pro	tta Leu gga Gly 40	gat Asp 25 aaa Lys	Leu 10 aca Thr tgg Trp	Val gga Gly aaa Lys	Thr gca Ala cca Pro	gat Asp aaa Lys 45	gat Asp 30 atg Met	Ile 15 aca Thr ata Ile	gta Val 999 Gly ata	96
ggg Gly tta Leu gga Gly	caa Gln gaa Glu att Ile 50	atc Ile ata Ile gaa Glu 35 gga Gly	Thr aag Lys 20 atg Met Gly ggm	Leu 5 gaa Glu agc Ser	Trp gct Ala ttg Leu atc Ile aaa	Cta Leu Cca Pro aaa Lys 55	tta Leu gga Gly 40 gta Val	Pro gat Asp 25 aaa Lys agm Xaa	Leu 10 aca Thr tgg Trp cag Gln	Val gga Gly aaa Lys tat Tyr	Thr gca Ala cca Pro gwt Xaa 60 tta	gat Asp aaa Lys 45 cat His	gat Asp 30 atg Met ata Ile	Ile 15 aca Thr ata Ile ccc Pro	Gly gta Val ggg Gly ata Ile	96 144
ggg Gly tta Leu gga Gly gaa Glu 65	caa Gln gaa Glu att Ile 50 wtc Xaa	atc Ile ata Ile gaa Glu 35 gga Gly tgt Cys	Thr aag Lys 20 atg Met ggt Gly ggm Xaa ata	Leu 5 gaa Glu agc Ser ttt Phe cat	Trp gct Ala ttg Leu atc Ile aaa Lys 70 gga	Cta Leu Cca Pro aaa Lys 55 gct Ala	tta Leu gga Gly 40 gta Val gaa Glu aat	Pro gat Asp 25 aaa Lys agm Xaa ggt Gly	Leu 10 aca Thr tgg Trp cag Gln aca Thr ttg	Val gga Gly aaa Lys tat Tyr gta Val 75 act	Thr gca Ala cca Pro gwt Xaa 60 tta Leu cag	gat Asp aaa Lys 45 cat His	Lys gat Asp 30 atg Met ata Ile gga Gly	Ile 15 aca Thr ata Ile ccc Pro	Gly gta Val ggg Gly ata Ile aca Thr 80 act	96 144 192

-203-

cca	gga Gly	atg Met	Asp	ggg Gly	cca Pro	aaa Lys	gtt Val 120	Lys	caa Gln	tgg Trp	cca Pro	cta Leu 125	Thr	gaa Glu	gaa Glu		384
		Lys										Glu			gga Gly		432
aaa Lys 145	Ile	gaa Glu	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160		480
					gac Asp												528
					aga Arg												576
					ggg Gly												624
					tat Tyr												672
					acc Thr 230												720
att Ile	aga Arg	tat Tyr	caa Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	caa Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro		768
					agc Ser												816
caa Gln	aat Asn	cca Pro 275	gaa Glu	yta Xaa	gtt Val	atc Ile	tac Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val		864
gga Gly	tca Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	gar Glu 295	aag Lys	cat His	aga Arg	gca Ala	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu		912
					aaa Lys 310												960
cag Gln	aaa Lys	gaa Glu	Pro	cca Pro 325	ttt Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1	800
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	acc Thr	ata Ile	aag Lys	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1	056

-204-

gtc aat gat ata cag aag tta gtg gga aaa ttg aat tgg gca agt caa Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
att tat cca ggg Ile Tyr Pro Gly 370	1116
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ggg cag cta aag gaa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa atk ata ggg Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Xaa Ile Gly 35 40 45	144
gga att gga ggt ttt atc aaa gta aga cag tat gat cag ata ctt gta Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Leu Val 50 55 60	192
gaa att tgt gga cat aaa gct ata ggt aca gta tta gta gga cct aca Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr 65 70 75 80	240
cct gtc aac ata att gga aga aat ctg ttg act cag att ggt tgc act Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr 85 90 95	288
tta aat ttt ccc att agt cct att gag act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336
CCA gga atg gat ggc cCA aaa gtc aaa caa tgg cCA ttg aCA gaa gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta atg gaa att tgt gca gaa wtg gaa aag gaa gga Lys Ile Lys Ala Leu Met Glu Ile Cys Ala Glu Xaa Glu Lys Glu Gly 130 135 140	432

WO 01/35316 PCT/US00/30863

-205-

						Pro					Asn				ttt Phe 160	480
	ata Ile				Asp										Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttt	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
	cca Pro															624
	gtg Val 210															672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	acm Xaa	cca Pro	999 Gly 240	720
	aga Arg															768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	att Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
	tct Ser 290															912
	cag Gln															960
	aaa Lys		Pro		Phe		Trp		ĞĨy	Tyr					Āsp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	caa Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aag Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 3 <u>5</u> 5	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttr Xaa	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
	tac Tyr 370															1116

WO 01/35316 PCT/US00/30863

-206-

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cct		atc										ata Ile				48
				Glu								gat Asp				96
tta Leu	gaa Glu	gaa Glu 35	atg Met	aat Asn	ttg Leu	cca Pro	gga Gly 40	aaa Lys	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	gjå aaa	144
												cag Gln				192
												ata Ile				240
												ctt Leu				288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggt Gly	cca Pro	aga Arg	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	acm Xaa	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	ata Ile	gaa Glu 135	atc Ile	tgc Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gam Xaa	sga Xaa	432
waa Xaa 145	att Ile	tca Ser	aaa Lys	mta Xaa	999 Gly 150	cct Pro	gam Xaa	wat Xaa	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528

-207-

			aat Asn 180											576
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			gat Asp											672
_		_	gca Ala	_	_	_		_						720
			cag Gln											768
			caa Gln 260											816
_			gaa Glu	_	_	_	_		_	_	_	_	_	864
			tta Leu											912
			ctg Leu											960
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gtc Val	Asn		ata Ile											1104
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<220>

WO 01/35316 PCT/US00/30863

-208-

<221> CDS <222> (0)...(297) <223> HIV Protease <221> CDS <222> (298)...(1116) <223> Portion of HIV Reverse Transcriptase <400> 114 cmt caa atm amt ctt tgg car mra ccc cta gtc cna awn nmm gkk agg Xaa Gln Xaa Xaa Leu Trp Gln Xaa Pro Leu Val Xaa Xaa Xaa Xaa Arg 48 ggg gca aat aag gaa gct cta tta gac aca gga gca gat gat mca gta 96 Gly Ala Asn Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Xaa Val tta gaa gaa atg wat tta cca gga aaa tgg aaa cca aaa atg ata ggg 144 Leu Glu Glu Met Xaa Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly gga att gga ggt ttt atc aaa gta agn cag tat gag cag ata ccc ata 192 Gly Ile Gly Gly Phe Ile Lys Val Xaa Gln Tyr Glu Gln Ile Pro Ile gaa atc tgt gga cat aaa gct ata ggt aca gta ttg gta ggm cct aca 240 Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Xaa Pro Thr cct gtc aac ata att gga aga aat ctg ttg act cag att ggt tgc act 288 Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr 90 tta aat ttt ccc att agt cct att gaa act gta cca gtg aaa tta aag 336 Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 105 cca gga atg gat ggc cca aaa gtt aaa caa tgg cca tta aca gaa gaa 384 Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aaa gaa ggg Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly 432 135 aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt 480 Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe 150 155 gcc ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe 170 aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtc caa tta gga 576 Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly ata cca cat cct gca ggg tta aaa aag aaa aaa tca gta aca gtg ctg 624 Ile Pro His Pro Ala Gly Leu Lys Lys Lys Ser Val Thr Val Leu 200

-209-

gac gtg ggt gat gca tat ttt tca gtt ccc tta gat aaa gac ttc agg Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Asp Phe Arg 210 215 220	672
aag tat act gca ttt tcy ata cct agt aca aac aat gag aca cca ggg Lys Tyr Thr Ala Phe Xaa Ile Pro Ser Thr Asn Asn Glu Thr Pro Gly _225 230 235 240	720
agt agg tat caa tac aat gtg ctt cca cag gga tgg aaa gga tca cca Ser Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro 245 250 255	768
gca ata ttc caa agt agc atg ata aaa atc tta gag cct ttt aga aaa Ala Ile Phe Gln Ser Ser Met Ile Lys Ile Leu Glu Pro Phe Arg Lys 260 265 270	816
caa aat cca raa att gtg atc tat cma tac mtg gat gat ttg tat gta Gln Asn Pro Xaa Ile Val Ile Tyr Xaa Tyr Xaa Asp Asp Leu Tyr Val 275 280 285	864
gga tct gac tta gaa ata gaa cag cat aga aca aaa ata gag gaa ctg Gly Ser Asp Leu Glu Ile Glu Gln His Arg Thr Lys Ile Glu Glu Leu 290 295 300	912
aga caa cat ctg ttg agg tgg gga ttt acc aca cca gac aag aaa cat Arg Gln His Leu Leu Arg Trp Gly Phe Thr Thr Pro Asp Lys Lys His 305 310 315 320	960
cag aar gaa cct ccg ttc ctt tgg atg ggt tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008
aaa tgg aca gta cag cct ata gtg ctg cca gaa aaa gac ags ttg rct Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Xaa Leu Xaa 340 345 350	1056
kca aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag Xaa Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
att tac tca ggg Ile Tyr Ser Gly 370	1116
<210> 115 <211> 1116 <212> DNA <213> Human Immunodificiency Virus (HIV)	
<220> <221> CDS <222> (0)(297) <223> HIV Protease	
<221> CDS <222> (298)(1116) <223> Portion of HIV Reverse Transcriptase	

-210-

	cct	00> : cag	g at	c ac e Th	t ct r Le	t tgg u Trp	g caa o Glr	a cga n Arg	a cco	c cto Leu	ı Val	aca Thi	a ata r Ile	a aag E Lys	g ata s Ile 19	a ggg e Gly		48
_	999 999	caç Glr	g ct Le	a aag u Lys 20	s Gl	a gct ı Ala	cta Lev	ata 1 Ile	gat Asp 25	aca Thr	ı qqa	gca Ala	a gat a Asp	gat Asp	aca Thi	a gtg Val		96
	tta Leu	gaa Glu	ga Gl: 3!	u Met	g agt	ata Ile	cca Pro	gga Gly	r Lys	tgg Trp	aaa Lys	cca	a aaa Lys 45	Leu	ata Ile	ggg Gly	1.	44
	gga Gly	att Ile 50	Gl	a ggt y Gly	ttt Phe	ato lle	aaa Lys 55	Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	Gln	gkg Xaa	ccc Pro	gta Val	19	92
,	gaa Glu 65	Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gct Ala	ata Ile	ggt Gly	mca Xaa	gtw Xaa 75	tta Leu	ata Ile	ggm Xaa	cct	aca Thr 80	24	40
:	cct Pro	gcc Ala	aac Asr	ata lle	att Ile 85	gga Gly	agg Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr	28	38
]	tta Leu	aat Asn	ttt Phe	Pro	Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	33	86
]	cca Pro	gga Gly	atg Met 115	Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aag Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gag Glu	38	14
Ī	aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	aca Thr	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	gga Gly	43	2
Ι	ag ys 45	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	48	0
. P	иa	Ile	Lys	Lys	Lys 165	gac Asp	Ser	Thr	Lys	Trp 170	Arg	Lys	Leu	Val	Asp 175	Phe	52	8
A	ga rg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gat Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	57	6
I	ta le	cca Pro	cat His 195	cct Pro	gca Ala	Gly 999	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624	4
А	sp	Val 210	Gly	Asp	Ala		Phe 215	Ser	Val	Pro	Leu	Asp 220	Glu	Asp	Phe	Arg	67:	2
Tr.	aa ys ' 25	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	Val	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240	720	0

-211-

att Ile	aga Arg	tat Tyr	cag Gln	tat Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	tgt Cys	agt Ser	atg Met	aca Thr	aaa Lys 265	ata Ile	tta Leu	gag Glu	ccc Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Glr	aat Asn	cca Pro 275	gac Asp	cta Leu	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	aaa Lys 310	tgg Trp	ggt Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aag Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cca Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
	tac Tyr 370															1116
<21:	0> 11 L> 11 2> DN 3> Hu	16 A	Immu	nodi	fici	ency	Vir	us (HIV)							
<221 <222	<213> Human Immunodificiency Virus (HIV) <220> <221> CDS <222> (0)(297) <223> HIV Protease															
<222	> CD !> (2 !> Po	98).	(1: n of	116) HIV	Rev	erse	Tra	nscr	ipta	se						
cct	> 11 cag Gln	atc a	act o	ctt Leu '	tgg (Irp (caa (Gln)	cga Arg	ccc Pro	ctc Leu 10	gtc . Val '	aca Thr	ata Ile	aag Lys	ata Ile 15	Gly aaa	48
Gly 999	cag (Gln)	cta a Leu 1	aag g Lys (20	gaa g Glu i	gct (Ala 1	cta 1 Leu 1	tta (Leu)	gat Asp ' 25	aca (Thr (gga (Gly	gca Ala	gat Asp	gac Asp 30	aca Thr	gta Val	96

-212-

tt: Le:	a gaa u Glu	a gaa 1 Glu 35	$_{1}$ Ile	a agt e Sei	cto Lei	g cca	gga 61 ₃ 40	/ Arc	tgg Trp	g aaa Lys	cca Pro	a aaa D Lys 45	Let	g ata	ggg Gly		144
Gly Gly	a att y Ile 50	: Gl	a ggt 7 Gly	ttt Phe	ato Elle	aaa Lys 55	Val	aag Lys	cag Gln	tat Tyr	gat Asp 60	Gln	ata Ile	ccc Pro	ata Ile		192
gaa Glu 65	ı Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	Ala	ata Ile	ggt Gly	aca Thr	gta Val 75	Lev	gta Val	ggm Xaa	Pro	aca Thr 80		240
Pro	gto Val	aac Asn	ata Ile	gtt Val 85	Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	ctt Leu	ggt Gly	tgc Cys 95	Thr		288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys		336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aag Lys	gtt Val 120	aag Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu		384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	ttg Leu 140	gaa Glu	aag Lys	gaa Glu	Gly 999		432
aaa Lys 145	Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160		480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	aca Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe		528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttt Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	cta Leu	gly aaa		576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	Gly 999	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu		624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	ttg Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg		672
aag Lys 225	tac Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aat Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240		720
att Ile	aga Arg	tat Tyr	Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	Gly	tca Ser 255	cca Pro		768
gca Ala	ata Ile	Phe	caa Gln 260	agt Ser	agc Ser	atg Met	Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	Pro	ttt Phe 270	aga Arg	aaa Lys	i	816

-213-

caa Gl:	a aat n Asr	cca Pro 275	Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	Gln	tac Tyr	gta Val	gat Asp	gac Asp 285	Leu	tat Tyr	gta Val	864
gga Gly	Ser	Asp	tta Leu	gaa Glu	ata Ile	999 Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	g Gln	cat His	ctg Leu	tgg Trp	aag Lys 310	tgg Trp	Gly aaa	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gat Asp	aaa Lys	aaa Lys	cat His 320	960
						ctt Leu										1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aag Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	tta Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
	tac Tyr 370															1116
<210> 117 <211> 1119 <212> DNA <213> Human Immunodificiency Virus (HIV)																
<pre><213> Human Immunodificiency Virus (HIV) <220> <221> CDS <222> (0)(297) <223> HIV Protease</pre>																
<22	1> CI 2> (2 3> Po	298).				erse	Tra	nscr	ipta	se						
cct	0> 11 caa Gln	atc	act Thr	ctt Leu 5	\mathtt{Trp}	caa Gln	Arg	Pro	Ile	Val	Thr	Ile	Lys	Ile	Gly 999	48
ggg ggg	caa Gln	cta Leu	aag Lys 20	gaa Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
tta Leu	gaa Glu	gaa Glu 35	atg Met	gat Asp	ttg Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aca Thr	cca Pro	aaa Lys 45	atg Met	ata Ile	gly ggg	144
gga Gly	att Ile 50	gga Gly	ggt Gly	ctt Leu	gtc Val	aaa (Lys ' 55	gta Val .	aga Arg	cag Gln	tat (Tyr)	gat Asp 60	cag Gln	ata Ile	ccc Pro	ata Ile	192

=1.

-214-

ga: Gl: 6!	u Ile	tgt Cys	gga Gly	a cat His	aaa Lys 70	Thr	ata Ile	a ggt e Gly	aca Thr	yta Val	Lev	a gta 1 Val	gga Gly	cct Pro	aca Thr 80		240
Pro	gco Ala	aac Asr	ata 1 Ile	att : Ile : 85	: Gly	aga Arg	aat Asr	ctg Leu	ttg Leu 90	Thr	cag Gln	g ctt Lev	ggt Gly	tgt Cys 95	act Thr		288
tta Leu	a aat 1 Asn	ttt Phe	ccc Pro	Ile	agt Ser	cct Pro	att	gaa Glu 105	Thr	gta Val	cca Pro	gta Val	aaa Lys 110	Leu	aag Lys		336
eca Pro	gga Gly	atg Met	Asp	ggc	cca Pro	aaa Lys	gtt Val 120	Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	Thr	gaa Glu	gaa Glu		384
aaa Lys	ata Ile 130	Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	ttg Leu 140	gaa Glu	aag Lys	gaa Glu	gga Gly		432
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	999 Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gtg Val	ttt Phe 160		480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe		528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly		576
ata Ile	cca Pro	cat His 195	cct Pro	gca Ala	gga Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu		624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gac Asp 220	aag Lys	gac Asp	ttt Phe	agg Arg		672
aaa Lys 225	tat Tyr	act Thr	gca Ala	ttt. Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	aca Thr	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	999 Gly 240		720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro		768
gca Ala	ata Ile	Phe	caa Gln 260	agc Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gat Asp	cct Pro	ttt Phe 270	aga Arg	aag Lys		816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	Ile	tgt Cys 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val		864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	Ile	999 Gly 295	cag Gln	cat His	aga Arg	Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	•	912

-215-

aga Arg 305	g Glu	cat His	ctg Leu	tgg Trp	aag Lys 310	Trp	Gly	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cac Glr	aaa Lys	gaa Glu	cct Pro	ccg Pro 325	Phe	ctc Leu	tgg Trp	atg Met	ggt Gly 330	Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aac Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
	tat Tyr 370	-														1119
<210> 118 <211> 979 <212> PRT <213> Human Immunodificiency Virus																
	0> 13		D	T1.	01	m\	**- 7	D	**- 7			_	_			
1	Ile			5					10	_		_		15		
Asp	Gly	Pro	Lys 20	Val	Lys	Gln	Trp	Pro 25	Leu	Thr	Glu	Glu	Lys 30	Ile	Lys	
Ala	Leu	Val 35		Ile	Cys	Thr	Glu 40		Glu	Lys	Glu	Gly		Ile	Ser	
Lys	Ile		Pro	Glu	Asn			Asn	Thr	Pro		Phe	Ala	Ile	Lys	
	50 Lys	Asp	Ser	Thr		55 Trp	Arg	Lys	Leu		60 Asp	Phe	Arg	Glu		
65 Asn	Lys	Arg	Thr		70 Asp	Phe	Trp	Glu		75 Gln	Leu	Gly	Ile	Pro	80 His	
Pro	Ala	Gly		85 Lys	Gln	Lys	Lys		90 Val	Thr	Ile	Leu		95 Val	Gly	
Asp	Ala		100 Phe	Ser	Val	Pro		105 Asp	Glu	Gly	Phe		Lys 110	Tyr	Thr	
Ala	Phe		Ile	Pro	Ser			Asn	Glu	Thr		125 Gly	Ile	Arg	Tyr	
Gln	Tyr		Val	Leu		135 Gln		Trp	Lys		140 Ser	Pro	Ala	Ile	Phe	
145 Gln	Ser	Ser	Met	Thr	150 Arg	Ile	Leu	Glu	Pro	155 Phe	Arg	Lys	Gln	Asn	160 Pro	
	Ile			165				-	170					175		
			180					185					190			
	Glu	195					200					205				
Leu	Leu 210	гуѕ	Trp	GIY	Phe	Thr 215	Thr	Pro	Asp	Lys	Lys 220	His	Gln	Lys	Glu	
Pro 225	Pro	Phe	Leu	Trp	Met 230	Gly	Tyr	Glu		His 235		Asp	Lys	Trp	Thr 240	
	Gln	Pro		Lys 245		Pro	Glu	Lys			Trp	Thr	Val	Asn 255		

Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Ala Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg Glu Ile Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys Asp Leu Ile Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr Asn Asp Val Lys Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile Val Ile Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile Val Gly Ala Glu Thr Phe Tyr Val Asp Gly Ala Ala Asn Arg Glu Thr Lys Leu Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu Thr Asp Thr Thr Asn Gln Lys Thr Glu Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp Ser Gly Leu Glu Val Asn Ile Val Thr Asp Ser Gln Tyr Ala Leu Gly Ile Ile Gln Ala Gln Pro Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln Leu Ile Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile Gly Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Ile Phe Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly Ile Pro His Pro Ala Gly Leu Lys Gln Lys Lys Ser Val Thr Ile Leu Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Gly Phe Arg Lys Tyr Thr Ala Phe Thr Ile Pro Ser Arg Asn Asn Glu Thr Pro Gly Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser Met Thr Arg Ile Leu Glu Pro Phe Arg Lys Gln Asn Pro Glu Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val Gly Ser Asp Leu Glu Ile

Gly Gln His Arg Ala Lys Ile Glu Glu Leu Arg Gly His Leu Leu Lys 745 740 Trp Gly Phe Thr Thr Pro Asp Lys Lys His Gln Lys Glu Pro Pro Phe 760 Leu Trp Met Gly Tyr Glu Leu His Pro Asp Lys Trp Thr Val Gln Pro 775 780 Ile Lys Leu Pro Glu Lys Asp Ser Trp Thr Val Asn Asp Ile Gln Lys 795 790 Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Ala Gly Ile Lys 805 810 Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr Glu 825 820 Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg 840 Glu Ile Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys 855 860 Asp Leu Ile Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr 870 875 Gln Ile Tyr Gln Glu Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala 885 890 Arg Met Arg Gly Ala His Thr Asn Asp Val Lys Gln Leu Thr Glu Ala 900 905 910 Val Gln Lys Ile Thr Thr Glu Ser Ile Val Ile Trp Gly Lys Thr Pro 920 925 Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp Glu Thr Trp Trp Thr 935 940 Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe Val Asn Thr 955 Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile Val 965 970 Gly Ala Glu

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